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FARM INJURIES*

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SIXTEEN thousand five hundred lives were lost in occupational accidents in the United States in 1948. Four thousand four hundred of these, or 26.6 per cent, were due to the hazards of farming. The death rates per 100,000 workers in mines, quarries, gas and oil wells and in construction were respectively three times and twice that of agriculture.[1] However, in actual number of fatal accidents, farming leads all other major industries (Table 1).

By recognition of the inherent dangers to which workers in other occupations are daily exposed and by the institution and enforcement of measures to promote safety both by management and by labor, other industrial death rates are steadily falling. Significant improvement has occurred even during the past five years. Between 1945 and 1948 the rate for miners and allied workers dropped from 187 to 154 per 100,000 employees; the rates for construction and transportation fell from 126 to 93 and from 68 to 48 respectively.[1-3] On the contrary, the occupational death rate among workers on farms was actually higher in 1948 than in 1945 (Table 2).

TABLE 1. *Total Number of Fatal Accidents and the Death Rates per 100,000 Workers in Major Industries in the United States in 1948.*

INDUSTRY	DEATHS	
	TOTAL	PER 100,000 WORKERS
Agriculture	4,400	55
Manufacturing	2,600	16
Construction	2,500	93
Service	2,200	15
Trade	1,500	14
Transportation	1,500	48
Mining, quarrying, gas and oil wells	1,400	154
Public utilities	400	29

Furthermore, fatal accidents form only a small proportion of the total. In a comprehensive survey made by the Department of Agriculture, covering 3000 odd counties in the United States in 1948,[4] the following estimation for the first four months of that year was given:

> Over a quarter of a million people who were living or working on farms were injured seriously enough to lose at least one day's time from their regular activities. The cost of medical, dental, and hospital care exceeded eleven million dollars and the total time lost was over six million days, including no allowance for the time lost by persons who were fatally injured or permanently and totally disabled.

TABLE 2. *Comparative Death Rates among Workers in Mines, Quarries, Gas and Oil Wells, in Construction, in Transportation and in Agriculture, 1945-1948.*

INDUSTRY	DEATHS PER 100,000 WORKERS			
	1945	1946	1947	1948
Mining, quarrying, gas and oil	187	163	167	154
Construction	126	105	96	93
Transportation	68	53	53	48
Agriculture	53	52	52	55

And this concerned four months of the year when farm accidents are very much less numerous than they are during the summer and autumn! Twenty million working days per year is a minimal estimate of the amount of time lost to agriculture as a result of farm accidents.

The purpose of this report is to present in some detail a series of 658 such accidents sustained in a rural section of New York State where dairy farming is the principal means of livelihood. The patients were treated at the Mary Imogene Bassett Hospital in Cooperstown during the years 1929-1948 inclusive. The accidents that occurred during the first of these two decades were discussed before the Section on Preventive and Industrial Medicine and Public Health at the Ninetieth Annual Session of the American Medical Association in St. Louis in 1939[5]; those sustained during the second period were reported to the American Association for the Surgery of Trauma in Atlantic City in 1949.[6]

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In the present survey the accidents in each of these two decades are discussed individually for comparison of one period with the other; they are also reviewed collectively for the establishment of over-all figures covering both decades.

Analysis of 658 Farm Accidents

Incidence

During the twenty years embraced by this study 3134 patients with serious injuries from all types of trauma were admitted to the Mary Imogene Bassett Hospital; 658 of these (20.9 per cent), or one fifth of all admissions due to accidents, were related to the hazards of farming.

Only 34 per cent of these patients had received professional care before arrival; 17 per cent had been given some first aid by laymen; 49 per cent had had no medical attention.

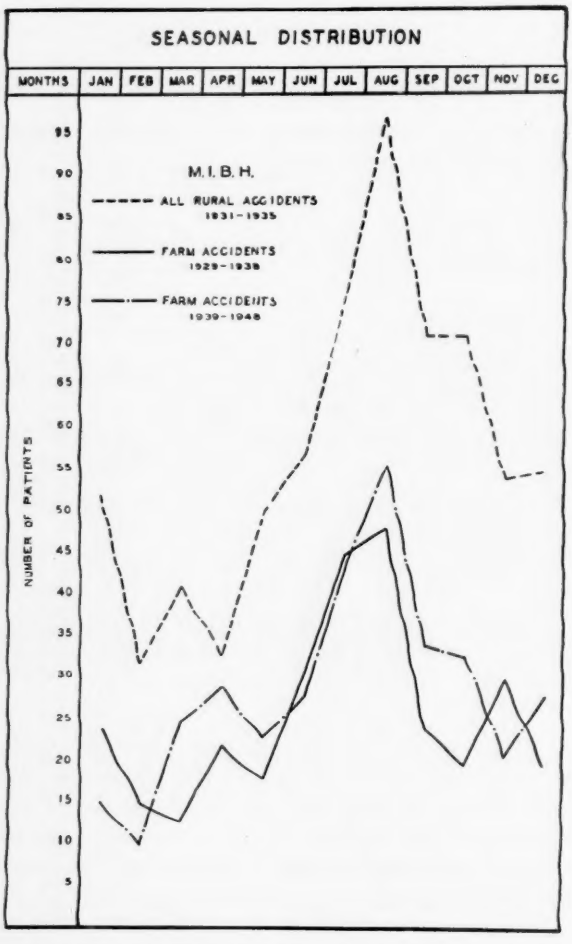

FIGURE 1. *Seasonal Distribution of Farm Accidents during the Decades 1929-1938 and 1939-1948 Compared with the Seasonal Distribution of All Rural Accidents from 1931 to 1935 (Reproduced from Calandruccio and Powers,[6] with the Permission of the Publishers).*

Nearly half the patients reached the hospital within two hours of the accident, and an additional 10 per cent arrived during the next four hours. Eight per cent were not admitted until after the lapse of a week. With no medical attention for many of these during this interim, serious complications were frequent.

Liability

Seventy per cent of the accidents in the first decade and 65 per cent in the second were due to carelessness of the person injured; 10 per cent were caused by carelessness of someone other than the patient. In other words, 75 to 80 per cent of all the accidents in both decades were preventable. About 15 per cent were unpredictable, and in the small group remaining liability for the accident could not be definitely allocated.

Seasonal Distribution

A marked increase in all rural accidents occurs during the summer and early autumn. Accidents due to farming, to motoring and to sports are responsible for the peak in August.[7] Curves representing the seasonal variation in farm accidents alone during each of the two decades in this study are very comparable to one another and are similar to the curve for all rural accidents reported previously (Fig. 1). The peaks during July and August are composed largely of accidents due to haying, those occurring during the repair and construction of buildings and those in which children are involved while at play around machinery in operation, men at work, and farm animals and buildings. Accidents in the course of routine chores maintain a fairly constant frequency throughout the twelve

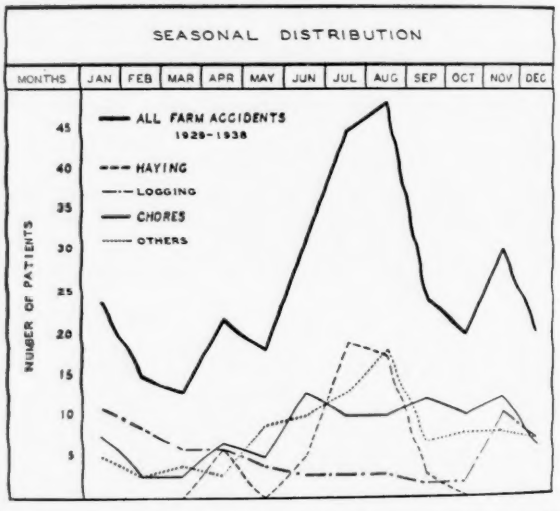

FIGURE 2. *Seasonal Variation of All Farm Accidents, 1929-1938, and Their Common Motivating Components (Reproduced from Powers,[5] with the Permission of the Publishers).*

months, whereas those associated with marketing of timber from wood lots and with the production of firewood occur most often during the late fall and winter (Fig. 2). Summer is the most hazardous season of the year on the farm, and late winter and early spring the most secure.

Location

During the years 1929-1938 the barn and barnyard were found to be the most dangerous areas on the farm (Fig. 3). Accidents in the pastures, fields and hayfields were next in order of frequency

FIGURE 3. *Location of 310 Farm Accidents during the Decade 1929-1938 (Reproduced from Calandruccio and Powers,[6] with the Permission of the Publishers).*

but were still less than half as common as those in the barn and barnyard. Seven per cent of the accidents occurred in the farmhouse and shed. These should perhaps be more properly designated as "home accidents," and yet they are generally considered to represent one of the hazards of rural living and are included by the National Safety Council among agricultural accidents. The "highway accidents" did not represent mishaps to farmers riding in motor vehicles for pleasure but were limited to those that took place on the highway during hours of work with animals or farm machinery. The close correlation in the frequency with which farm accidents occurred in the same localities during the decade 1939-1948 is striking (Table 3). The first group was analyzed by me, and the second by Dr. R. A. Calandruccio,[6] without collaboration during the actual perusal of the hospital records and tabulation of the data. The average figures for both decades are recorded in Table 3.

Etiology

At least two factors contribute to the etiology of all agricultural injuries except those resulting from falls: a motivating activity and a causative agent.

TABLE 3. *Location of 310 Farm Accidents during 1929-1938 and 348 Accidents during 1939-1948.*

SCENE OF ACCIDENT	PERCENTAGE OF FARM ACCIDENTS		
	1929–1938	1939–1948	AVERAGE AGE
Barn or barnyard	50.0	51.6	50.8
Fields and pastures	21.0	22.1	21.5
Woods	13.5	8.5	11.0
House and shed	6.8	8.1	7.5
Highway	4.2	4.7	4.4
Others	4.5	5.0	4.8

During the twenty years embraced by this study, routine farm chores were responsible for nearly a third of the 658 accidents; logging accounted for a fifth; haying and mishaps to children at play were each responsible for an essentially equal number (Table 4). "Assault and suicide" may be questioned as hazards of farming, but both are occasionally induced by the lonely life of poverty and solitude that many farmers lead in distinctly rural areas and hence are included in this survey.

Numerous falls on slippery, icy and uneven ground, without any specific causative agent, and a few miscellaneous agents, such as rusty nails, barbed-wire fences, thorns and splinters that have not been classified separately, accounted for a third of all the accidents. Injuries due to farm animals were next in order of frequency; three fourths of these were caused by horses, and a fourth by cows and bulls. Tools, scythes, axes, pitchforks, manure forks and other implements were responsible for a sixth of the injuries. Machinery, of which rotary saws, ensilage cutters and mowing machines are by far the most mutilating, was the specific agent

TABLE 4. *Activities Responsible for 658 Farm Accidents, 1929-1948.*

ACTIVITY	NO. OF ACCIDENTS	PERCENTAGE
Chores	186	28.2
Logging	130	19.5
Haying	112	17.0
Children at play	93	14.2
Repair and construction buildings	31	4.8
Assault or suicide	18	2.8
Others	88	13.4

in 12 per cent of the accidents. Farm vehicles were next in order of frequency (Table 5).

In 1942 Creevey[8] presented a report of 370 farm accidents from the Mary McClellan Hospital in Cambridge, New York. The methods of farming in that part of the State are similar to those in the vicinity of Cooperstown. The motivating activities and etiologic agents responsible for the accidents in Creevey's study correspond very closely with those reported above. However, in the great agricultural areas of the midwestern and north central regions of the United States, where mechanized farming has been extensively developed, machines rank second among the leading causes of accidents. In these areas 28 per cent of the accidents due to machinery are associated with tractors, and 9 per cent with combines and threshing machines. In the Far West and South, animals assume second place as they do among the dairy farming communities of central New York. Throughout the nation, falls rank first as a cause of farm accidents.

TABLE 5. *Etiologic Agents in 658 Accidents.*

AGENTS	No. OF ACCIDENTS	PERCENTAGE
Falls or miscellaneous agents	236	35.8
Animals	115	17.5
Tools or implements	113	17.2
Machines	79	12.0
Vehicles	71	10.8
Falling trees	35	5.3
Heat or cold	9	1.4

Classification of Injuries

The 658 patients included in this survey sustained 1527 injuries recorded according to the *Standard Classified Nomenclature of Disease*. These are tabulated by percentages in order of frequency for each decade separately, and for both together, in Table 6. In actual numbers there were 488 fractures, of which 134, or 27.4 per cent, were compound. Lacerations were next in frequency. Divisions of tendons, nerves and blood vessels and partial or complete amputations of fingers, hands, forearms and legs were common. Puncture wounds were less frequent but were often complicated by extensive and serious infections. Many patients received multiple lesions of bones and soft parts in combination.

Of more interest in a study of farm accidents is the topographic distribution of the injuries and fractures sustained. This was determined for the first decade, and the data are presented in Figure 4. The frequency of all injuries involving each anatomic subdivision is recorded by percentage in this chart in the black columns above the horizontal lines; below these lines in the shaded columns are recorded in the same manner all fractures of the bones of the same subdivisions. The findings indicate that the upper extremities received 50 per cent more total injuries than the lower; fractures alone occurred with equal frequency in both.

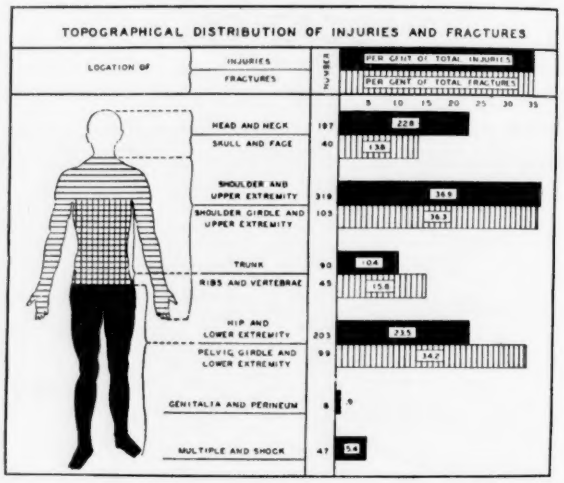
TOPOGRAPHICAL DISTRIBUTION OF INJURIES AND FRACTURES
LOCATION OF
INJURIES
FRACTURES
NUMBER
PER CENT OF TOTAL INJURIES
PER CENT OF TOTAL FRACTURES
0 5 10 15 20 25 30 35
HEAD AND NECK 197 22.8
SKULL AND FACE 40 13.8
SHOULDER AND UPPER EXTREMITY 319 36.9
SHOULDER GIRDLE AND UPPER EXTREMITY 103 36.2
TRUNK 90 10.4
RIBS AND VERTEBRAE 45 15.8
HIP AND LOWER EXTREMITY 203 23.5
PELVIC GIRDLE AND LOWER EXTREMITY 99 34.7
GENITALIA AND PERINEUM 8 .9
MULTIPLE AND SHOCK 47 5.4

FIGURE 4. *Topographic Distribution of Injuries and Fractures Sustained in Farm Accidents during the Years 1929-1938 (Reproduced from Powers,[5] with the Permission of the Publishers).*

TABLE 6. *Classification of 1527 Recorded Injuries in Order of Frequency of Occurrence.*

CLASSIFICATION	PERCENTAGE OF FARM INJURIES		
	1929–1938	1939–1948	AVERAGE 1929–1948
Fractures	33.7	30.0	31.7
Lacerations	14.5	14.0	14.2
Divisions or amputations	10.6	5.9	8.2
Contusions	7.8	6.2	7.0
Incised or punctured wounds	7.4	6.6	7.0
Abrasions	6.1	4.9	5.5
Concussion	4.1	5.7	4.8
Dislocations	4.1	4.1	4.1
Burns or frostbites	3.5	2.4	2.9
Shock	2.1	1.1	1.6
Compressions	0.6	0.7	0.7
Gunshot wounds	0.6	1.1	0.9
Foreign bodies	0.5	2.4	1.4
All others	4.3	15.0	9.9

Period of Hospitalization

During the first decade embraced by this survey, 1929-1938, the average period of hospitalization as a result of farm accidents was eighteen and three-tenths days; during the years 1939-1948 the average was fourteen and one-tenth days. This decrease of 23 per cent represents an average of four and two-tenths days per farmer patient — a distinct saving of both time and money. Open reduction and internal fixation of fractures, the liberal use of chemotherapeutic agents and antibiotics, and prompt ambulation whenever possible after injury have been responsible for abbreviating the

convalescence in the hospital during the past decade.

Analysis of Fatal Cases

During the years 1929-1938 there were 16 deaths among 310 patients admitted to the Mary Imogene Bassett Hospital because of occupational injuries sustained in farming. During 1939-1948 there were 3 deaths among 348 patients with injuries of comparable severity. Two of these were moribund on admission, and the third succumbed to massive pulmonary embolism (Table 7). Five of the fatal accidents in the first decade and 2 in the second occurred during the performance of routine chores. Farm animals were responsible for a fifth of the fatal accidents in the first group and for all 3 in the second.

The gratifying improvement in the mortality from serious farm injuries during the years 1939-1948 may be attributed in part to a more thorough understanding of the physiologic alterations in the human economy effected by severe trauma, to the greater availability of blood and blood substitutes, to the extensive use of chemotherapeutic agents and antibiotics whenever indicated, and to the employment of anticoagulants for the prevention and treatment of thrombosis.

TABLE 7. *Analysis of Fatal Farm Accidents.**

CAUSE OF DEATH†	No. OF CASES	CONTRIBUTING ACTIVITY	No. OF CASES	CONTRIBUTING AGENT	No. OF CASES
1929-1938 (310 patients):					
Fracture-dislocation of cervical spine	4	Chores	5	Animal	3
Compound depressed fracture of skull	3	Logging	4	Heat (fire)	3
Extensive burns	3	Haying	3	Vehicle	2
Multiple injuries and shock	2	Children at play	2	Falling tree	2
Tetanus	1	Repair of building	1	Machine	1
Peritonitis	1	Suicide	1	Firearm	1
Bacteremia due to *Staphylococcus aureus*	1			Others or none	4
Coronary thrombosis	1				
Totals	16		16		16
1939-1948 (348 patients):					
Multiple injuries and shock	2	Chores	2	Animal	3
Pulmonary embolism	1	Haying	1		
Totals	3		3		3

*Total mortality, 1929-1948, 2.9 per cent.

†Mortality 5.1 per cent in 1929-1938 and 0.8 per cent in 1939-1948 groups.

SUMMARY

Six hundred and fifty-eight patients with serious injuries due to farm accidents, representing a fifth of all the admissions caused by trauma, were treated at the Mary Imogene Bassett Hospital during the years 1929 to 1948.

Such accidents showed a definite variation in seasonal incidence with a peak during July and August for which haying, repair and construction of buildings, and children at play were largely responsible.

Routine chores were the most dangerous motivating activities throughout the year. Farm animals, tools and machinery contributed their share of injuries in that order. Falls were numerous.

Exactly half the accidents occurred either in the barn or in the barnyard.

Nearly 50 per cent of the patients reached the hospital in two hours.

Fractures comprised approximately a third of the 1527 recorded injuries. Extensive lacerations, divisions of nerves, tendons and blood vessels and partial or complete amputations of extremities were common.

The average period of hospitalization was eighteen and three-tenths days during the first ten years of the survey and fourteen and one-tenth days during the second.

The mortality fell from 5.1 per cent in the first decade to 0.8 per cent during the second.

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URETHANE TOXICITY*

Report of a Case of Hepatic Necrosis Apparently Due to Urethane

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WIDE experience in the use of urethane (ethyl carbamate) has accumulated since the appearance of the original report of Paterson et al.[1] in 1946. It is now generally accepted that the drug has proved of some use in chronic myelogenous leukemia and less constantly in chronic lymphatic leukemia.[1-10] Results in acute and subacute leukemia[2, 3, 4, 7, 9] and polycythemia vera[5] have been disappointing.

With notable exceptions other malignant diseases have responded poorly or not at all.[4, 9, 11, 12] Hodgkin's disease, lymphosarcoma, mixed salivary-gland tumor, lymphoepithelioma and various carcinomas have occasionally regressed,[1, 9, 13] as have mycosis fungoides[9, 14] and endocrine-independent prostatic carcinoma.[12, 15] In multiple myeloma reports have indicated striking symptomatic improvement in about 30 per cent of cases, with reversal of serum proteins and bone-marrow abnormalities in some.[16-18]

TABLE 1. *Reported Incidence of Toxic Effects of Urethane in Order of Frequency.*

SYMPTOM	PERCENTAGE OF CASES*
Nausea or vomiting, or both	50.0
Anorexia	40.0
Leukopenia	16.0
Thrombocytopenia	14.5
Diarrhea	13.0
Drowsiness	10.0
Aplastic anemia	6.0
Mental symptoms	4.0
Lack of normal leukocytic response to infection	1.8
Weight loss	0.9
Renal damage (1 case)	0.5
Hepatic necrosis with death (1 case)	0.5
Headache	0.5

*Percentage figures derived from reports in which toxic symptoms are mentioned.

DOSAGE AND CLINICAL TOXICITY

Daily doses have varied from 1 to 13 gm. for periods of nine days to ten and a half months.[1] Until recently the largest published total amount was 683 gm. in two hundred and ninety-nine days.[7] The schedule most commonly employed in the treatment of leukemia has been 2 to 4 gm. daily in divided doses for one to three months, often followed by a maintenance dose of 1 or 2 gm. Harrington and Moloney,[18] however, have recently reported the use of larger quantities for periods up to thirty months.

The toxic effects that have been attributed to urethane are listed in Table 1.

We were able to find in the literature 8 deaths attributed to urethane, as follows: agranulocytosis, 1 case[19]; aplastic anemia, 2 cases[1, 20]; hepatic necrosis, 1 case[15]; and pneumonia without normal leukocytic response to infection, 4 cases.[21]

GASTROINTESTINAL SYMPTOMS

Severe gastrointestinal symptoms have appeared after relatively small amounts of the drug.[9] Serious vomiting, however, has occurred after several months of therapy.[1] Creskoff[7] found that nausea and vomiting was often prevented by intravenous administration of the drug. Berman and Axelrod[9] considered the gastrointestinal symptoms to be local irritative phenomena not requiring cessation of therapy. Enteric-coated urethane tablets have appeared to be helpful.[1, 18]

NEUTROPENIA

Neutrophil counts of less than 4000 have been reported after as little as 3 gm. a day for eighteen days[6] and as much as 295 gm. in seven and a half months.[1] The bone marrow of individual patients has shown marked variation in susceptibility to urethane. In fact Paterson [1] found that from 19 to 134 gm. given in eleven to thirty-six days at various dosage levels was required to produce a fall of 20,000 leukocytes in chronic myeloid leukemia. Patients without leukemia apparently have shown greater susceptibility to the drug.[1, 9, 14, 16]

APLASTIC ANEMIA

In fatal cases of aplastic anemia 1 patient received 13 gm. daily for twenty-four days,[1] and another 5 gm. for twenty-five days.[20] A number of nonfatal cases have been recorded.[1, 7, 9]

RENAL TOXICITY

In a case reported by Kennedy, Nathanson and Aub[14] red and white cells and albumin appeared in the urine after 3 or 4 gm. daily for seventeen days. The abnormal urinary findings disappeared two weeks after cessation of treatment. The urine remained clear when urethane therapy was reinstituted. This is of interest since renal glomerular lesions have been produced with urethane in mice.[22, 23]

*From the Medical and Pathological Services, Veterans Administration Hospital, West Roxbury, Massachusetts.

Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. The statements made and conclusions drawn by the authors are a result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

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Liver Toxicity

The only previously reported case of hepatic necrosis was one of prostatic carcinoma reported by Huggins, Yu and Jones.[15] The patient received an average dose of 9 gm. for thirty-three days, and 14 to 16 gm. daily for the last fifteen days for a total of 297 gm. Harrington and Moloney[18] reported a patient with multiple myeloma who showed icterus after urethane therapy consisting of 6 gm. a day for four and a half months. The jaundice subsided in 11 weeks and was attributed to infectious hepatitis from blood transfusion.

Other Symptoms

Other reported toxic effects of urethane have included mental symptoms, headache[24] and rapid weight loss.[9]

The following case represents the second reported case of hepatic necrosis appearing during urethane therapy:

Case Report

E. D., a 47-year-old grocer, was first admitted to the Veterans Administration Hospital, West Roxbury, Massachusetts, on March 2, 1944, with lobar pneumonia, from which he recovered in 16 days. On this occasion, he had no complaints referable to the skeletal system. The blood pressure was 140/80; the white-cell count was 12,500, and the red-cell count 3,500,000.

He was next admitted on December 1, 1947, complaining of pain in the right hip and back of 5 months' duration. X-ray films of the skeleton showed compression of the tenth thoracic vertebra and a 4-mm. defect in the parietal region of the skull. Examination of the blood disclosed a white-cell count of 11,600, with 50 per cent neutrophils, 40 per cent lymphocytes and 4 per cent monocytes. The blood nonprotein nitrogen was 44 mg. and the serum protein 12.1 gm. per 100 cc., with an albumin of 4.6 gm., and a globulin of 7.5 gm. Examination of the urine revealed a + test for albumin; the test for Bence-Jones protein was negative. Bone-marrow smears demonstrated numerous immature plasma cells, and the diagnosis of multiple meyloma was made.

The patient was fitted with a back brace, and on January 1, 1948, urethane therapy, 1.0 gm. by mouth three times daily in gelatin capsules, was begun. At this time no side effects of the drug occurred.

After discharge the patient was maintained on 3.0 gm. of urethane a day by mouth. When seen at monthly intervals he complained only of occasional mild pain in the lower back. During the next 18 months gradual increase in the extent of osseous lesions occurred. Myeloma cells were consistently present in the bone marrow, amounting to 38 to 63 per cent of the nucleated elements. The serum globulin increased to 16.9 gm. per 100 cc. Mild anemia persisted, but leukopenia never occurred.

On June 8, 1949, the dose of urethane was increased to 6.0 gm. daily. For the first time the liver edge was felt 6 cm. below the right costal margin. The blood pressure was 186/120.

The final admission occurred on August 14, because of recurrence of severe pain in the lower back and pain in the left anterior portion of the chest, nausea, vomiting and generalized abdominal pain. There was splinting of the muscles of the back, and rib tenderness. The abdomen was obese and soft, and the liver edge was felt 4 cm. below the right costal margin. Feces were brown.

During the first 22 days of hospitalization, low-grade elevation of the temperature was observed. On September 5 an episode of urinary infection with bacteremia due to *Aerobacter aerogenes* occurred, and was treated successfully with streptomycin. Testosterone propionate, 50 mg. daily, was given intramuscularly on August 19, 20 and 21, followed by 25 mg. daily until August 29. Methyl testosterone tablets, 50 mg. daily, were then given until September 22.

On October 1 anorexia, nausea and vomiting developed. The patient was found to have ascites. Urethane was omitted. Icterus became evident the next day, and on October 4 examination revealed bile but no urobilinogen in the urine. The white-cell count was 11,000 with 82 per cent neutrophils, 16 per cent lymphocytes, 1 per cent monocytes and 1 per cent eosinophils. The red-cell count was 3,100,000, with a hemoglobin of 9.5 gm. The alkaline phosphatase was 7.2 Bodansky units, and the total serum protein 6.3 gm. per 100 cc., with an albumin of 2.1 gm. The blood cholesterol was 102 mg. per 100 cc. with 87 mg. of esters, and the serum bilirubin 20 mg. per 100 cc. (13 mg. direct and 7 mg. total). The cephalin-flocculation test was +++, and the thymol turbidity was normal; the prothrombin was 27 per cent of normal.

At this time the abdomen was distended, and dilated loops of small bowel were visible on x-ray study. Intubation was not helpful.

During the next 6 days the patient became increasingly jaundiced, and the liver enlarged further. He lapsed into coma and died on October 13.

Autopsy, performed 2½ hours after death, revealed a fairly well nourished man with deep-yellow skin and scleras. There was +++ pitting edema of the ankles and 1590 cc. of brownish-yellow abdominal fluid, but no hydrothorax. The heart weighed 340 gm.; the myocardium and valves were normal, and the coronary arteries had many small atheromatous plaques but were patent. The aorta was moderately atherosclerotic, with scattered calcified plaques in the abdominal portion.

The lungs weighed 390 and 410 gm. and were pale pink and well aerated in all lobes, except for minimal peripheral atelectasis in the lower lobes posteriorly.

The spleen weighed 190 gm., with a smooth capsule and deep-red, slightly soft and friable parenchyma. The pancreas and adrenal glands were normal.

The liver weighed 1960 gm., with a smooth capsule beneath which were several small (0.4 to 0.8 cm.) hemorrhages. The cut surface was deep purple red, with indistinct lobular markings.

The gall bladder was slightly distended, with a slightly thickened pink-white serosa. In the lumen were 43 cc. of pale-brown bile and twenty angular brown stones, 0.6 to 1.2 cm. in diameter. The bile ducts were all patent. The cystic duct was not dilated, nor was the common duct. The ampulla was free of obstruction.

The kidneys weighed 190 and 300 gm., the capsules stripping easily from deep-red smooth surfaces.

The vertebral bodies were reddish purple and partially or almost completely lacking in cancellous bone trabeculae. Although none were collapsed, many of the dorsal vertebras, especially the first lumbar, were appreciably narrowed. The sternal, costal and iliac bone marrow was also soft, and the femoral and tibial marrow yellow.

Permission for examination of the head was not obtained.

Microscopical examination revealed a diffuse infiltration of the vertebral and costal bone marrow by plasma-cell myeloma and similar infiltration of less degree of the sternal, iliac and femoral bone marrow. The tumor cells were of the mature type. No amyloidosis was found. The renal tubules contained bile-stained casts and desquamated epithelium in places, but the kidneys were otherwise not remarkable. The heart showed several very small foci of interstitial myocardial fibrosis and an area of calcification in the epicardium. Histopathological features of the liver are described below.

The pathological diagnoses were: plasma-cell myelomatosis, subacute central hemorrhagic necrosis and bile stasis of the liver, cholelithiasis, chronic cholecystitis, bile nephrosis, atherosclerosis of the aorta and coronary arteries, pulmonary emphysema (slight), extramedullary hematopoiesis (slight) of the spleen, ascites (1590 cc. of fluid), peripheral edema and jaundice.

On cursory inspection of the liver the impression obtained was one of an extensive central hemorrhagic necrosis, in which only the peripheral third or less of the lobule remained intact. In one section the central liver cells had disappeared completely in places, leaving empty cords, or persisting as

faded or shrunken pale shadowy cells, some showing many small cytoplasmic vacuoles (Fig. 1). Often in the peripheral parts of the depleted central areas were two or three large foci of fresh hemorrhage (Fig. 2). These were either lacking or so extensive as to fill the central area. In a few places the remaining central liver cells showed acute (almost infarct-like) necrosis with polymorphonuclear leukocytes invading the cells, early karyolysis, dissociation and fibrin thrombi in the sinuses around a partly or completely thrombosed central vein (Fig. 3). A few polymorphonuclear leukocytes could be seen in the necrotic cells or reoriented in the fibrin clot in the central vein. No bacteria were seen. Granular iron-positive brown pigment was present in small to moderate amounts in the cytoplasm of the viable peripheral liver cells. The Kupffer cells of the depleted central areas were also full of iron-positive brown pigment, but none was seen in the portal fibrous tissue.

In a second section the central depletion was so uniform as to suggest strongly an element of passive congestion. However, fatty metamorphosis was seen in only one lobule (as large droplets sparsely scattered through the central area). A third section contained four round nodules of regenerated liver cells 1 to 4.5 mm. in diameter, the two larger each having a narrow fibrous band around one side (Fig. 4). Elsewhere, portal fibrous tissue was slightly increased in only a few places, the collagen fingering off among the liver cells, with sometimes a small, loose collection of lymphocytes. A slight increase in small bile ducts had occurred in a few foci. Retention of bile in the canaliculi was widespread in this section, whereas it was present in only one lobule in the first section and almost completely lacking in the second. Occasional polymorphonuclear leukocytes were present in or around the small bile ducts in all three sections; the ducts contained no bile, but the lumen was usually extremely narrow, suggesting that the stasis was in part due to swelling of the epithelium. Swelling of the portal fibrous tissue may also have been a factor, although the tissue did not appear edematous. The increased bile stasis in the third section seems to have been due to the slight degree of cirrhosis present.

There was an acute diffuse central hemorrhagic necrosis in addition to evidence of endothelial damage in the form of fibrin thrombi of a few central veins; a much older focal damage of very slight degree (in one out of three sections); a variable amount of stasis in the bile canaliculi; and slight hemosiderosis (as seen in patients who have received many transfusions).

FIGURE 1. *Section near the Center of the Liver Lobule, Showing Vacuolation of Degenerating Centrolobular Liver Cells.*

FIGURE 2. *Average Lobule, Showing Narrow Peripheral Fringe of Viable Liver Cells and Two Hemorrhagic Foci.*

DISCUSSION

Although there was extensive terminal liver destruction and presumably some centrolobular endothelial injury, the changes described cannot be regarded as specific. Such livers are also seen at autopsy in lobar pneumonia, heart failure with bronchopneumonia, and many other conditions. The relatively late onset of the bulk of the damage and its symmetrical central distribution indicate a considerable element of passive congestion or circulatory stasis.

Although it was not proved that this patient's hepatic necrosis was due to urethane, this was con-

sidered the likeliest explanation. He did not receive blood or plasma at any time. Methyl testosterone must be considered as a possible cause of liver damage in this case in view of recently reported jaundice during administration of the drug.[25] However, as the predominate lesion in the testosterone cases was bile stasis, with minimal liver-cell damage, it is believed that the pathological changes in the case reported above were quite different. Histologic findings were not reported by Huggins, Yu and Jones[15] in their patient, who died with the clinical picture of severe hepatic derangement after urethane.

Evidence that urethane in large doses can adversely affect the liver has been reported. Sollman[26] stated that the drug, given in large doses, resulted in vacuolar degeneration of hepatic epithelium. Doljanski and Rosin,[27] studying the effect of toxic agents on the livers of rats, found that lethal doses of urethane produced pronounced damage to portal venules and sinusoidal capillaries, with extravasation of plasma and blood cells, and vacuolization of liver cells. Prolonged action of smaller doses caused atrophy and disappearance of liver cells in the central portions of the lobules. They concluded that changes in liver cells were probably the result of primary vascular damage. This was supported by the work of Landis,[28] who found that urethane produced increased capillary permeability. Howe and Tedeschi[29] reported findings similar to those of Doljanski and Rosin. We have been unable to find reference in the literature to hepatic necrosis as a part of the course of multiple myeloma.[30-34]

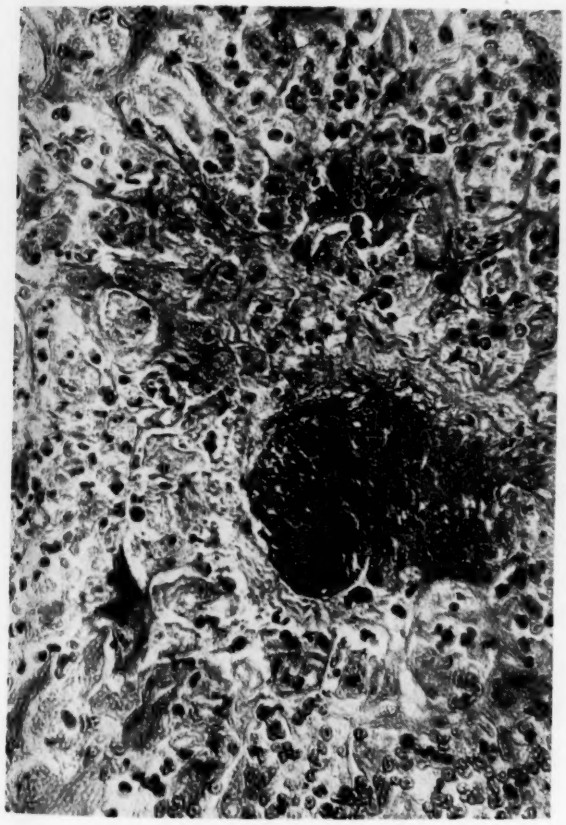

FIGURE 3. *Fibrin Thrombus in the Central Vein and Adjoining Sinusoids of the Liver Lobules.*

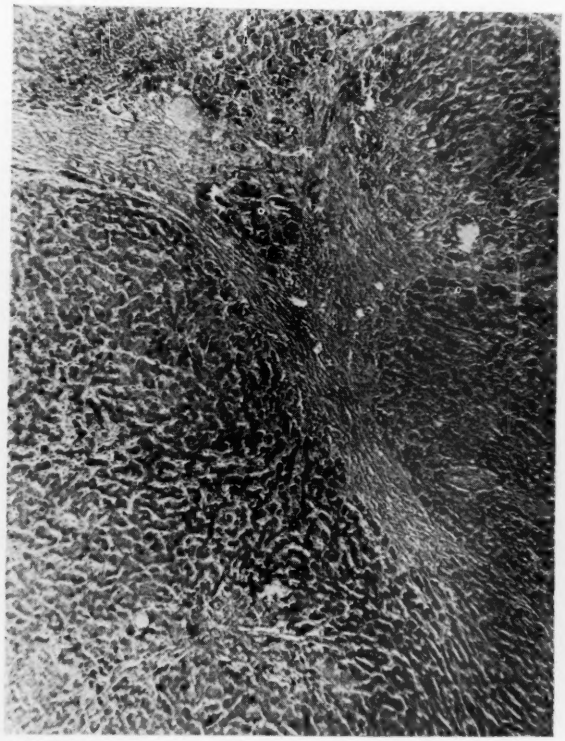

FIGURE 4. *Section of the Liver Showing the Only Appreciable Fibrotic Focus, with Adjacent Nodularity.*

Experimentally, changes in other organs and tissues have been produced with urethane. These have included hypertrophy of the adrenal glands and decrease in size of lymphatic tissue suggesting the "alarm reaction" of Selye,[35, 36] congestion of lungs, liver, and spleen and hyperplasia of the mesenchyme in the lungs, spleen, myocardium and liver.[29] Of especial interest was the production of adenomatous lesions in the lungs[37] and, in susceptible inbred mice, of lesions resembling human glomerulonephritis.[22, 23] Alkalosis, with increased carbon dioxide content, has been reported.[38, 39]

The effect of urethane on cell growth and metabolism has been extensively studied, and has been reviewed by Haddow and Sexton,[40] Webster[19] and Hirschboeck et al.[4] Mitosis was abolished for eight to twelve hours.[41, 42] Urethane was excreted

from the blood of normal mice almost completely in twenty-four to twenty-eight hours, and studies with labeled carbon have shown that 90 per cent of the carbonyl carbon was exhaled as carbon dioxide.[43]

Summary and Conclusions

The toxicity of urethane is reviewed.

Gastrointestinal symptoms, which have occurred in 50 per cent of cases, have sometimes been alleviated by the use of parenteral or enteric-coated medication.

Hematologic effects have been serious. Leukopenia, occurring in 16 per cent of treated cases, has appeared somewhat more frequently in nonleukemic patients. Aplastic anemia has occurred.

These toxic effects have followed various doses and total amounts of the drug.

A case of fatal hepatic necrosis in a patient receiving large doses of urethane in the treatment of multiple myeloma is reported. Duration of therapy was twenty-one months, with daily dose of 6 gm. for four months preceding death — a total of 2259 gm. This is the second reported case of fatal liver derangement in a patient receiving urethane.

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ANEURYSMS OF THE SPLENIC ARTERY*

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THE recognition of aneurysms of the splenic artery is important since death from spontaneous hemorrhage ultimately occurs in the majority of cases and since these aneurysms may be completely excised at an elective time without jeopardizing the blood supply of vital organs. Because of the rarity of this lesion aneurysm of the splenic artery is almost never considered in the differential diagnosis of diseases that produce similar signs and symptoms. Elective surgical extirpation of the aneurysm has been successful in a high percentage of cases, but the number of patients operated upon before rupture has occurred has been small. The experience of surgeons in the treatment of ruptured aneurysms has been disheartening, and the mortality rate is very high when this disaster occurs. At the present time the diagnosis of splenic-artery aneurysm is established either at the time of abdominal exploration or at post-mortem examination in cases of fatal internal hemorrhage. In addition a small number are found incidentally at routine post-mortem examination. It is unfortunately true that aneurysms of the splenic artery often do not cause symptoms or signs before they suddenly rupture. Nevertheless, a significant number of them present clinical findings that make diagnosis possible, and it is in this group that elective operation may be safely carried out before severe intra-abdominal hemorrhage occurs.

A large aneurysm of the splenic artery was recently encountered at operation, and this case is reported below. The purpose of this communication is to call attention to the clinical manifestations and treatment of splenic-artery aneurysms. If the possibility of this diagnosis is kept in mind a greater number of elective aneurysmectomies may be carried out, and the high mortality that follows rupture may be avoided.

CASE REPORT

A 64-year-old man entered the hospital on November 26, 1948, because of abdominal pain of 3 days' duration. One week before admission generalized weakness had developed. He was examined by a physician and was told that he had anemia and an enlarged spleen. Immediately after this examination he experienced moderately severe, steady abdominal pain in the left upper quadrant, which was increased by deep inspiration and relieved by lying down. The pain gradually diminished during the next 2 days but became sharp and lancinating after a hot bath. He was then hospitalized.

Ten years previously he had had a massive hemorrhage from the gastrointestinal tract, necessitating several blood transfusions. Subsequent roentgenologic studies had demonstrated a duodenal ulcer. After this bleeding episode he was maintained on a bland diet and was free of symptoms except for occasional postprandial epigastric discomfort. The remainder of the history was noncontributory.

Physical examination revealed a rather short, stocky, elderly man in no marked distress. Positive findings, other than a moderate degree of pallor, were limited to the abdomen. There was a poorly defined fullness in the left upper quadrant. On palpation there was a firm, somewhat tender, slightly irregular, rounded mass extending from the left costal margin downward to the iliac crest; medially, it extended to the midline. The mass moved with respiration. It did not pulsate. There was no demonstrable peritoneal fluid, and no other masses or organs were felt. The blood pressure was 130/70.

FIGURE 1. *Anteroposterior Film of the Abdomen, Showing a Rounded Homogeneous Soft-Tissue Mass without Calcification in the Upper Segment of the Left Side of the Abdomen. The mass displaces the air-filled stomach superiorly and medially. The central portion of the mass is at the level of the twelfth thoracic vertebra.*

Examination of the blood disclosed a red-cell count of 3,700,000, with 11.2 gm. of hemoglobin, and a white-cell count of 11,800, with 81 per cent neutrophils. The platelet count was normal. The sedimentation rate was 15 mm. in 1 hour, and the serum bilirubin 0.7 mg. per 100 cc. The bromsulfalein test demonstrated 1 per cent retention of the dye in 1 hour.

A plain film of the abdomen showed a somewhat globular soft-tissue mass without calcification in the left hypochon-

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driac region (Fig. 1). An intravenous urogram demonstrated anterior rotation of the left kidney, with downward displacement by a mass that was extrinsic to its upper pole. Barium studies of the upper gastrointestinal tract showed that the stomach was markedly compressed and displaced anteriorly, medially and upward (Fig. 2). Roentgenograms of the thorax demonstrated elevation of the left hemidiaphragm. The precise nature of the mass was not determined preoperatively, but it was believed that the findings were consistent with the diagnosis of a cyst of the spleen. Pancreatic cyst was the alternative diagnosis, but was not favored because of the

FIGURE 2. *Lateral Film of the Upper Abdomen, Showing the Barium-Filled Stomach Displaced Anteriorly by a Large Mass, Which is Closely Applied to the Posterior Wall.*

relatively anterior position of the central portion of the mass as seen on lateral films of the abdomen.

On December 7 exploratory celiotomy was carried out through a left-rectus-muscle-splitting incision. A large, firm, nonpulsating mass was found lying posterior to the stomach and displacing it forward. The spleen was displaced upward and posteriorly, and the splenic flexure of the colon was depressed. The gastrocolic ligament was divided, and dense adhesions between the mass and the posterior wall of the stomach were dissected. The posteromedial aspect of the mass seemed to rest directly upon the aorta. At this point it was believed that the lesion was perhaps an aneurysm of the aorta in an unusual location, but because of the intimate association of the tumor with the pancreas it was concluded to be a pancreatic cyst. During the dissection accidental rupture of the mass occurred, resulting in profuse hemorrhage and extrusion of blood clots, which identified the true nature of the lesion. The absence of pulsation of the aneurysm was explained by the large amount of clotted blood within it. The medial portion of the base of the aneurysm was grasped, and compression was made along the superior border of the pancreas, where the proximal portion of the splenic artery was thought to be. This maneuver brought about temporary control of the bleeding. Two heavy braided-silk ligatures were placed rather blindly in this region through pancreatic tissue in order to effect a mass ligature that would include the proximal splenic artery. A similar mass ligature through pancreatic tissue was made on the distal side of the aneurysm. This permitted momentary visualization of the interior of the sac, and the arterial lumens were seen. Excision of the aneurysm was accomplished with removal of a segment of the body of the pancreas approximately 8 cm. in lenth. The splenic artery was then identified with certainty as the site of origin of the aneurysm. Had the correct diagnosis been considered before operation an initial direct approach to the proximal portion of the splenic artery, with ligation of the artery, would have been carried out, thus avoiding the subsequent difficulties encountered. The proximal and distal cut ends of the artery were secured with additional ligatures. During the period of hemorrhage the blood pressure had become unobtainable, and the pulse was rapid and thready. Blood transfusions were given under pressure. At the time hemostasis had been established the blood pressure was 80/40, and the pulse was

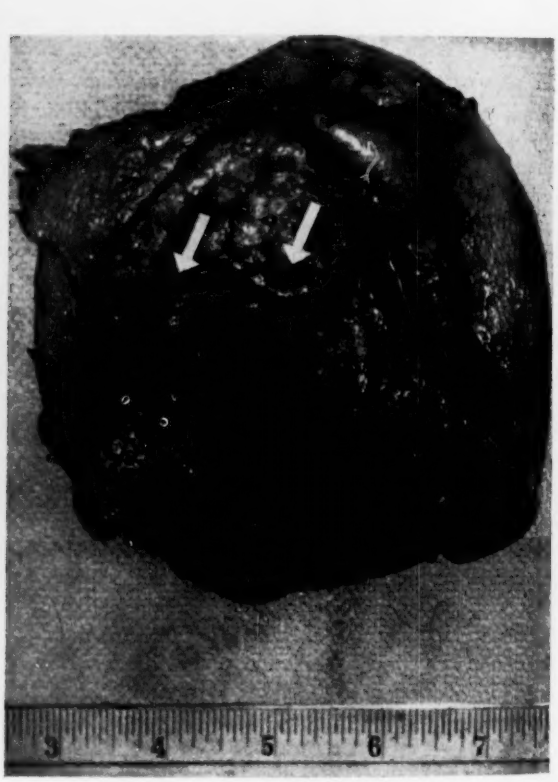

FIGURE 3. *Photograph of the Excised Aneurysm of the Splenic Artery, Showing the Interior of the Aneurysmal Sac. Arrows indicate the orifices of the splenic artery.*

120 per minute. The spleen was left in situ, and the isolated tail of the pancreas was not removed because the marked blood loss and temporary period of shock made it undesirable to prolong the procedure. The abdomen was closed, two Penrose drains being placed in the upper end of the incision, one in the region of the splenic pedicle and the other in the region of the ligated proximal end of the splenic artery, since it was expected that a pancreatic fistula might develop; 2500 cc. of blood was given during the procedure, and the blood pressure rose to 120/70 before the end of the procedure.

During the postoperative course a small pancreatic fistula developed. This was satisfactorily treated by frequent change of dressings and application of protective ointment to the skin. Repeated determinations of the fasting blood sugar

and serum diastase showed no variation from normal. At no time were there signs of peritoneal irritation or pain in the left upper quadrant, and it was believed that splenic necrosis had not occurred. The patient was discharged on January 1, 1949, with a persistent small fistula necessitating daily change of the dressing. When he was seen on February 23 the fistula had closed completely.

Thereafter he was well until December 2, when he reentered the hospital with recurrent gastrointestinal bleeding. Barium studies of the upper gastrointestinal tract revealed evidence of a duodenal ulcer for which he was treated medically. He was discharged 1 week later, improved, to follow a bland ulcer diet.

The pathological report of the excised specimen was as follows:

> The specimen consists of a segment of the splenic artery from which arises a large saccular aneurysm measuring 15 by 13.8 cm. In the wall of the aneurysm is an irregular tear measuring 14 cm. in length. There is an attached segment of pancreas measuring 8.5 by 3.5 by 2.2 cm. The outer surface of the sac is roughened in areas by fibrous tags. Microscopically, the wall of the aneurysm consists of compactly arranged layers of fibrous connective tissue. There is a chronic inflammatory infiltration. (Figure 3 shows the interior of the sac.)

Pathogenesis and Pathology

Almost any large or medium-sized artery in the abdomen may give rise to an aneurysm. Marrone[1] collected 77 cases of aneurysm of the renal artery. Rosenthal[2] collected 69 cases of aneurysms of the hepatic artery and 5 of the cystic artery. Laipply[3] reviewed 33 reports of aneurysms of the celiac artery. There have been a few recorded cases of aneurysm of the superior mesenteric, left gastric, pancreaticoduodenal, right colic and uterine arteries. Exclusive of the aorta, the splenic artery is the most common vessel in the abdomen from which aneurysms arise, approximately 150 cases having been recorded since the original description by Crisp[4] in 1847. Baumgartner and Thomas,[5] in 1924, collected 40 cases reported during the previous fifty years. In 1939 Machemer and Fuge[6] reviewed 83 cases. Sherlock and Learmonth,[7] in 1942, reviewed 124 collected cases. These authors found that a correct clinical diagnosis had been made in only 10 cases. Surgical procedures had been carried out in 38 cases, and 20 patients had survived operation. Cosgrove, Watts and Kaump,[8] in 1947, reviewed 107 of 144 cases in the literature.

There are three major causes of aneurysm of the splenic artery. Arteriosclerotic aneurysms are the most common and are characterized by atheroma formation and calcification in the aneurysm wall. They usually arise along the course of the main artery. Mycotic aneurysms are produced by embolism from vegetations on the heart valves and are usually found in the branches of the artery. In some cases the aneurysm develops from a congenital defect in the wall of the splenic artery, usually at a point of branching. It is interesting that 2 cases of splenic-artery aneurysm have been reported in association with congenital aneurysm of the circle of Willis.[7]

In addition to these groups, 4 cases have been reported subsequent to trauma, but in only 1, with direct gunshot injury, is there definite evidence of the causal relation of preceding trauma. A few aneurysms of the splenic artery have been found in the presence of Banti's disease. This relation appears to be only coincidental. Syphilis has been frequently cited as a cause, but syphilitic arteritis has been demonstrated microscopically in only 2 cases. Splenic-artery aneurysms have a curious predilection for becoming manifest during pregnancy. Lennie and Sheehan[9] collected 20 cases of rupture during pregnancy, almost all of which occurred in the last trimester. It has been suggested that the rise in intra-abdominal pressure concomitant with the advance of pregnancy predisposes to the formation of an aneurysm at the site of a congenital defect in the splenic artery.

The incidence of aneurysm of the splenic artery in 58,000 collected autopsies has been found to be 0.05 per cent.[10] The aneurysms may be single or multiple. In 84 cases Cosgrove and his associates[8] found 22 with multiple aneurysms. The size of the aneurysm in recorded cases has varied from 1 to 15 cm. in diameter, with an average of 3.4 cm.

As the aneurysm enlarges it encroaches upon surrounding structures to which it forms dense adhesions. Bertrand and Clavel[11] theorize that the aneurysm wall becomes fissured, producing a local hematoma. Organization of the clot, with formation of surrounding dense adhesions, follows. There is further hemorrhage into the adhesions, and the process is repeated until final rupture results. Massive rupture into the peritoneal cavity is the most common outcome. The aneurysm may rupture into the stomach or colon and occasionally ruptures into the retroperitoneal tissues.

Diagnosis

Before Rupture

Small unruptured aneurysms produce no symptoms and may be found only incidentally at autopsy. Larger aneurysms produce symptoms that are not usually of diagnostic value. Pain is the most frequent complaint. It may be severe and paroxysmal or mild, simulating the pain of chronic cholecystitis, chronic pancreatitis or peptic ulcer. The patient often obtains relief by stooping or lying down. Vomiting is frequently present owing to either involvement of the celiac plexus or irritation of the posterior wall of the stomach. There may be persistent leakage of blood from the aneurysm into the stomach or colon manifested by anemia, and melena or occult blood in the stool. The aneurysm may rarely cause pressure atrophy of the pancreas, resulting in the presence of undigested fat in the stool.[12]

Large aneurysms can occasionally be detected by physical examination if the possibility of the diagnosis is kept in mind. Palpation of the abdomen may reveal a mass in the left upper quadrant; expansile pulsation of the mass is commonly

present. Brockman[13] has stressed the importance of abdominal auscultation. Frequently, a bruit is heard over the left side of the abdomen and over the lower ribs posteriorly. Splenomegaly is a common finding and was noted in 18 of 43 cases reviewed by Baumgartner and Thomas.[5]

Roentgenologic studies are of prime importance. Until the present time calcification in the wall of the aneurysm has been the factor leading to the diagnosis by roentgenographic methods.[14] However, as demonstrated in the case presented above, calcification is not always present. Calcific deposits in the aneurysm form a round or oval shadow of increased density in the upper segment of the left side of the abdomen. The periphery is delineated by a thin line of calcification, which may be interrupted in one or more places creating a "cracked eggshell" appearance. The central portion is faintly mottled. The exact position may be determined by gastrointestinal barium studies and excretory or retrograde urography. By these methods the lesion is found to occupy a position posterior or posteromedial to the middle portion of the stomach, above the splenic flexure of the colon and superior to the upper pole of the left kidney. The center of the aneurysm is usually at the level of the twelfth thoracic or first lumbar vertebra. The roentgenographic picture may be similar to that of pancreatic cysts; however, in the latter calcification is rare.

After Rupture

Massive rupture may be the first evidence of an aneurysm of the splenic artery, or there may have been preceding symptoms for a period varying up to twenty-two years. In some cases rupture may be considered to occur in two stages.[13] There is an initial warning hemorrhage into the lesser peritoneal cavity, producing pain in the epigastrium accompanied by vomiting and tenderness in the upper abdomen. Clotting quickly occurs in this location, and a latent period follows, with regression of symptoms. Massive rupture occurs from one to fifty days later.

With massive rupture there is sudden severe pain in the upper abdomen referred to the left shoulder, persistent vomiting with tenderness and muscular rigidity in the epigastrium. As blood flows through the foramen of Winslow down the right side to the iliac fossa the pain becomes generalized, and the picture of internal hemorrhage develops with varying degrees of shock. Death in untreated cases results within twenty-four hours. Less frequently there is massive hematemesis or the passage of copious bright-red blood in the stool because of rupture into the stomach or colon or both organs simultaneously.

After rupture the diagnosis is most often confused with perforated peptic ulcer, rupture with ectopic pregnancy, acute pancreatitis, mesenteric thrombosis or embolism and acute intestinal obstruction. In late pregnancy it is usually thought to be rupture of the uterus or premature separation of the placenta with concealed hemorrhage. With the rapidly developing picture of intra-abdominal hemorrhage, massive transfusion and immediate operation are indicated although it may not be possible to make a definite diagnosis at this time. The correct diagnosis may not be determined even at operation unless it is kept in mind that, in the absence of trauma, cancer and rupture with ectopic pregnancy, a likely source of intraperitoneal hemorrhage is ruptured aneurysm of the splenic artery. The true source of bleeding was not determined in 25 per cent of the cases of aneurysm of the splenic artery in which abdominal operation was performed prior to 1942.[7] In this group such procedures as salpingectomy, cesarean section, gastroenterostomy or exploratory laparotomy were carried out. Death invariably resulted.

Treatment

All patients in whom the diagnosis of aneurysm of the splenic artery has been made should undergo operation for elective removal of the aneurysm because of the probability of rupture. Cosgrove and his associates[8] found that in 22 collected cases in which a direct attempt was made to eradicate the aneurysm, 17 patients survived operation. However, the results of treatment after rupture have been discouraging. I have been able to find only 3 reported cases of survival after massive rupture.[13, 15, 16] Proper diagnosis and the utilization of liberal blood transfusion could have saved many others.

Machemer and Fuge[6] recommend as the treatment of choice removal of the aneurysm together with the spleen and if necessary a segment of pancreas. Sherlock and Learmonth[7] also consider the ideal treatment to be removal of the spleen and the segment of artery from which the aneurysm has arisen. It has been felt that interruption of the splenic artery might produce necrosis of the spleen if that organ is left in situ. However, simple ligation of the splenic artery has been utilized in certain cases of portal hypertension without clinical evidence of necrosis of the spleen.[17] Ligation of the splenic artery in dogs produces a marked diminution in size of the spleen, but necrosis does not occur.[18] Sufficient blood for nutritive purposes will reach the spleen via the short gastric arteries. Therefore, in certain cases in which it seems unwise to prolong the time of operation the spleen may safely be left in situ. In some cases cure has been achieved by ligation proximal and distal to the aneurysm or by proximal ligation alone. Marsupialization, with packing of the aneurysm, has been uniformly unsuccessful.

At operation, after rupture has occurred, blood and clots are found to be welling down from some

obscure source in the upper abdomen, most often from the foramen of Winslow. The gastrocolic ligament must be incised, and the splenic, hepatic and celiac arteries explored. Frequently, an incision of the lower abdomen has been made with the presumptive diagnosis of rupture with ectopic pregnancy. When no source of bleeding is found in the pelvis the incision must be extended, and the omental bursa explored. In late pregnancy cesarean section should be carried out before excision of the aneurysm is attempted since the enlarged uterus prevents adequate exposure of the region of the splenic artery.

Summary

A case of an unusually large aneurysm of the splenic artery is presented, with the clinical and roentgenologic findings. At operation the aneurysm was successfully excised. Aneurysm of the splenic artery should be considered in two particular situations: when a mass of the upper abdomen of obscure origin is found (the findings may be similar to those of pancreatic cyst or cyst of the spleen) and when there is severe intra-abdominal hemorrhage in the absence of trauma, cancer or a source of bleeding in the female pelvis. Diagnosis is facilitated by the presence of a bruit heard over the left side of the abdomen or lower ribs posteriorly, splenomegaly and expansile pulsation when a mass is present. The roentgenologic findings are often characteristic. Elective removal of aneurysms of the splenic artery is indicated because of the likelihood of rupture, which is attended by a high mortality.

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THE EARLY TREATMENT OF COMMON COLDS WITH AN ANTIHISTAMINE-HISTADYL*

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A SERIES of articles on the use of antihistaminic drugs in the prevention and early treatment of common colds has appeared since the first paper by Brewster[1] in 1947. Several early and very optimistic medical reports were quoted widely in lay periodicals. These did much to stimulate heavy over-the-counter sales of antihistamine drugs in the winter of 1949-50. In more recent reports[2, 3] the trend of opinion has been against the efficacy of antihistamines in the treatment of the common cold. In contrast to some of the earlier reports, the studies of Cowan and Diehl[2] and Feller et al.[3] were well controlled and therefore seem to be more significant. It is believed that the following controlled study will contribute to the solution of this problem.

METHODS AND MATERIALS

The entering Freshman Class at Oberlin College — 617 men and women students living in nine dormitories — was divided into three groups. Each dormitory contained representatives of all three groups. Group A (236 subjects) received an antihistaminic drug. The drug used was thenylpyriline hydrochloride (Histadyl‡) administered in 50-mg. doses as a fine, white powder in plain, colorless gelatin capsules. Students were urged to keep capsules on hand and to start their use at the earliest symptom of a cold. They were instructed to repeat the medication at four-hour intervals for a minimum of four doses and up to ten doses if symptoms persisted. Printed directions were provided, giving detailed instructions.

Group B (203 subjects) received a plain, colorless capsule containing white, powdered starch, identical in appearance to those administered to Group A students, and were issued the same instructions as the students in Group A. During part of the study a trace of quinine sulfate was added to impart a bitter taste to the starch. Group C (178 subjects) abstained from all medication for prophylaxis or early treatment of colds.

A supply of Histadyl and placebo capsules was kept in each dormitory after an initial issue of 10 capsules to each student in the "A" and "B" groups.

The students in all groups were surveyed by questionnaire to determine the presence of allergies or chronic nasal sinus infections that might result in inaccurate reporting. In such circumstances the student was eliminated from the study (Table 1). At the end of the study certain other students were eliminated who had been irregular in reporting or unco-operative or who for any reason had not been able to continue in the study during the entire year. The final total of students on whom the report is based was 297 — 110 in Group A, 100 in Group B and 87 in Group C.

"Weekly Report Cards" were sent to each student. Upon their return, the data were transcribed to "Individual Master Cards." At the end of the study, each Master Card revealed one student's experience with colds for the entire period of the study, thirty-one weeks. The questions asked, the forms used and the type of statistical information given below are all patterned closely after those devised and used in the Students' Health Service at the University of Minnesota and reported recently by Cowan and Diehl.[2]

Those who handled the statistics were composed of several volunteer workers who tabulated individual weekly reports on the individual summary cards for each student, and one office worker who collected the data from the summary cards, placing them on large summary sheets, which were used for final tabulation. All these persons knew that subjects in Groups A and B were receiving

TABLE 1. *Number of Students in Each of the Three Groups.*

CLASSIFICATION	GROUP A (TREATED)	GROUP B (PLACEBO)	GROUP C (CONTROL)
Students who began study	236	203	178
Students eliminated because of allergy or sinusitis	68	39	21
Students eliminated because of non-co-operation, irregular reporting, reaction to drug and so forth ...	58	64	70
Students who completed study	110	100	87

TABLE 2. *Hospitalization for Respiratory Infections in Each of the Three Groups.*

GROUP	NO. OF STUDENTS	STUDENTS HOSPITALIZED FOR RESPIRATORY INFECTIONS	AVERAGE PERIOD OF HOSPITAL CARE
		%	*days*
A (treated)	110	19	4.7
B (placebo)	100	14	3.2
C (control)	87	24	5.0

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capsules and that students in Group C were reporting illness but receiving no medication. None of the workers knew the difference between capsules A and B, or that one of them was a placebo. The information given to the workers involved, to the house directors distributing the capsules and to the students themselves was that the two types of capsules, identical in appearance, contained different combinations of medicine. There was no secret of course about subjects in Group C, who received no medication.

Table 2 shows the only objective measure of results obtained in the use of Histadyl. The percentage of students in each group hospitalized for the treatment of respiratory infections during the year and the average number of days of care per hospitalized student are indicated. The students in Group B (receiving placebo capsules) had the lowest rate of hospital care and the fewest number of days of care per student hospitalized.

A summary of information furnished by the students appears in Tables 3 and 4. Table 3 shows that the average number of colds per student dur-

TABLE 3. *Number of Colds in Each Group.*

GROUP	AVERAGE NO. OF COLDS PER STUDENT DURING YEAR	PERCENTAGE OF GROUP WITH NO COLDS DURING YEAR
A (treated)	1.4	13.6
B (placebo)	1.2	11.0
C (control)	1.3	9.0

ing the year, as well as the percentage in each group who had no colds, in the three groups of students were very similar.

In Table 4 is shown the students' opinion of the severity of colds experienced and the severity judged by the writer on the basis of symptoms reported. The students' comparison with previous colds is also given. All these statistics show a degree of parallelism between the two Groups (A and B) receiving capsules. The control subjects (Group C) showed somewhat wider variations, but in no case do calculations show the differences to be "statistically significant." The last item in Table 4 gives the percentage of incipient colds that students reported as aborted or "prevented" by the medication taken. Here again there was no important difference between the group taking the antihistamine and those taking placebo capsules.

TABLE 4. *Classification of Colds.*

CLASSIFICATION	GROUP A (TREATED)	GROUP B (PLACEBO)	GROUP C (CONTROL)
	%	%	%
Student's opinion of severity:			
Mild	49.0	47.6	47.2
Moderately severe	30.5	36.9	36.3
Severe	17.8	14.3	13.9
Very severe	2.5	1.0	2.4
Severity of colds based on symptoms reported:			
Mild	73.5	76.6	82.2
Moderately severe	16.5	16.9	10.3
Severe	6.3	5.3	6.0
Very severe	3.4	1.0	1.5
Student's opinion of comparison with previous colds:			
Milder	59.3	45.4	33.0
Same	32.4	41.6	53.8
More severe	8.3	13.0	13.2
Shorter	82.3	80.6	69.2
Longer	17.7	19.4	30.8
Colds aborted or "prevented" by medication	20.9	19.2	—

CONCLUSIONS

This study presents no evidence that the antihistamine used (Histadyl) had any important effect in aborting or ameliorating the colds observed among the subjects studied.

The use of two different control groups provided valuable data and demonstrates anew the important psychologic effect of taking medication, whether placebo or other.

I am indebted to Drs. Donald W. Cowan and John H. Dingle for their advice in the planning of this study and to Dr. George F. Badger for reviewing the statistical data obtained.

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MEDICAL PROGRESS

SEROLOGIC TESTS IN THE DIAGNOSIS OF INFECTIOUS DISEASES

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GREAT advances have been made of late in the diagnosis, control and treatment of infectious diseases through the combined efforts of practicing physicians, laboratory workers and public-health workers. Foremost among these advances have been the development and standardization of laboratory diagnostic procedures, which are being used routinely. However, some procedures are still so highly specialized that competent technicians are required for their satisfactory performance. This, coupled with the high cost and scarcity of reagents, makes it prohibitive for most laboratories to offer these procedures as a routine service. For instance, the isolation and identification of virus and rickettsial agents are still research procedures. On the other hand, there are many serologic procedures providing useful information concerning infectious agents rather quickly, easily and inexpensively that many laboratories can offer to the practicing physician as a regular service. It is the purpose of this paper, therefore, to point out serologic tests that are readily available, their uses and their limitations.

SEROLOGIC TESTS

Serologic tests are used in the diagnosis of disease on the assumption that the development of antibodies against a particular infectious agent, or some of its products, is evidence that a patient is suffering or has suffered from an infection due to that particular agent. This assumption is based on two postulates: antibodies are specific and their formation is always induced by a specific stimulus. However, in defining specificity one must remember that the antigens of disease-producing organisms are complex in structure, and certain identical antigenic components can occur even in supposedly unrelated organisms. It is this sharing of antigenic components by dissimilar organisms that gives rise to cross-reactions, such as the Weil-Felix reaction, in which a particular carbohydrate is present in both the typhus rickettsia and certain strains of proteus.[1] Furthermore, an infection may so stimulate antibody production that a rise in antibody titer is brought about not only against the newly introduced antigen but also in the titer of antibody already present against another antigen. This is known as an anamnestic reaction. So far as formation of antibody by a specific stimulus is concerned, one must keep the prozone phenomenon in mind. This reaction, as yet unexplained, appears in a few strongly positive serums that give negative reactions when whole serum is used but positive reactions when dilutions of the same serum are employed.

Recovery of an agent from infected tissues along with demonstration of an increase in specific antibodies is the most conclusive diagnostic evidence available. However, recovery of an infective agent may be difficult, impractical or even impossible. Correlation of laboratory and clinical findings in certain infectious diseases has shown that serologic procedures are significantly conclusive even though the organism is not recovered. Therefore, immunologic tests should be done on the blood serum obtained during the *early* stages of the disease and again during convalescence or upon recovery. The presence of specific antibodies is of particular significance if blood specimens taken during the acute phase are negative and those taken during convalescence are positive. Should an acute-phase specimen be positive, the demonstration of a significant rise in the specific antibody titer during the course of the disease and convalescence is of particular import. A single specimen, therefore, is of little value. One taken early in the acute phase may be negative or may have such a low titer that no significance can be attached to it. One taken in the convalescent phase, even though positive, may be difficult to interpret because it is necessary to know not only the patient's previous experience with the infecting agent but also the frequency of positive tests in the population group to which the patient belongs, and the titer that can be considered within normal limits. The various combinations of reactions and their interpretations are listed in Table 1. Furthermore, it might be added at this point that rarely, if ever, is the antibody titer related to the degree of the patient's infection, to his immunity or to the prognosis of the case.

Since demonstration of a rise in antibody titer is necessary to corroborate a clinical impression of a case when an infecting agent cannot be recovered, the diagnosis frequently can be made only in retrospect and after recovery. It might therefore be considered that serologic testing is of little value to the practitioner concerned with the treatment of a case during the acute phase and is only of academic interest. This may be true generally, but in some

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cases, as in the follow-up study of treated patients with syphilis, periodic serologic tests are most essential. Retrospective confirmation or establishment of diagnosis will help to sharpen the clinician's diagnostic acumen and definitely confirm the patient's experience with the infecting agent for future reference. Serologic tests are of inestimable value to epidemiology and public health.

Precipitation, Agglutination and Complement-Fixation Tests

All serologic reactions depend on a union of the antibody in the serum with the antigen for which it has a specific chemical affinity. This union is the fundamental reaction, but it cannot be detected unless secondary reactions take place, which depend upon the physical state of the antigen and the conditions of the test.[3] If the antigen is in solution and antibody is added, a precipitate may form, if electrolytes are present. If the antigen is particulate (bacteria or colloidal particles coated with a soluble antigen), agglutination may occur when antibody is added in the presence of electrolytes. If complement is present when union of antigen and antibody occurs, it may be fixed by the antigen-antibody complex, and its fixation can be tested by the addition of sensitized sheep cells. This type of test must be used when the antigen-antibody combination does not produce a visible reaction as with virus infections.

Neutralization Test

The neutralization test is based on the principle that active virus, when mixed with specific antiserum, is rendered incapable of infecting susceptible cells. This principle was established with vaccinia by Sternberg[4] in 1892 and has come to be a mainstay in virus work. Neutralization tests are always costly in time and materials and frequently are difficult to interpret. Furthermore, no single technic is applicable to all agents. Each technic represents a compromise in the selection of various factors that influence the final result; among these are the choice of the indicator, the route of inoculation, the source of virus, the type of antiserum, the use of constant dilutions of serum with serial dilutions of virus or vice versa, the time and temperature of incubation of virus-antiserum mixture and the age of the inoculated animals. The test is usually carried out by titration of a constant amount of virus with varying dilutions of serum; however, serial dilutions of virus mixed with a constant amount of serum may be employed and have been found particularly useful in the study of neurotropic viruses.

In the performance of a test, serial dilutions of serums from acute and convalescent phases are set up in parallel, and a constant amount of virus is added. After incubation, the virus-serum mixtures are then inoculated into susceptible animals via a predetermined effective route. A 50 per cent end point or LD_{50}* is then calculated for each.[5]

In a positive test serum drawn during the convalescent phase shows a significantly enhanced protective effect or a significantly lower LD_{50} as compared to that of the acute phase. The significance of the difference between the LD_{50} of the acute-phase serum and that of the convalescent-phase serum is measured usually by the neutralization index,[6] which is the antilogarithm of the difference between the LD_{50}'s. For example, if the acute-phase serum dilution protecting 50 per cent of the animals is 10^{-9}, the LD_{50} or logarithm of the dilution is 9. Similarly, if the 50 per cent end point of the convalescent serum is $10^{-7.2}$, the LD_{50} is 7.2. The difference of these LD_{50}'s is 1.8, the logarithm of the neutralization index. Converting the logarithm to the antilogarithm, the neutralization index is obtained — namely, 63.1.

TABLE 1. *Combinations of Reactions to Serologic Tests with Their Interpretations.**

COMBINATION	SERUM DRAWN DURING ACUTE PHASE	SERUM DRAWN DURING CONVALESCENT PHASE	CONCLUSION
1	Negative	Negative	Disease not due to organism tested
2	Negative	Positive	Disease presumably due to organism tested
3	Positive	Positive (significant rise in titer)	Disease persumably due to organism tested
4	Positive	Positive (no significant rise in titer)	Contact with organism tested at some time in past, with no relation to present illness; first serum drawn too late in course of disease; second serum drawn too early in course of disease.
5	Not tested	Negative	Disease not due to organism tested
6	Not tested	Positive	Interpretation impossible, unless titer of convalescent specimen is at least as high as that usually found in persons recently recovered from the disease in question; in such cases a presumptive serologic diagnosis may be made on the basis of these suggestive findings.

*Based on data of Cheever.[2]

*Statistically derived estimate of the dilution (in logarithms) of serum that, when mixed with a fixed amount of virus and introduced into a susceptible animal, will produce a characteristic end point (pathologic lesion or death) in half the animals.

If only a single specimen is available, it can be run against a known negative serum; however, the finding of neutralizing antibodies in the single specimen cannot be regarded as significant. Mild missed cases are known to occur frequently, and in certain communities a considerable proportion of normal residents may have antibodies to the infectious agent under consideration.

The neutralization test has been used extensively for many years in the diagnosis of central-nervous-system infections by neutrotropic viruses. The test animal used generally is the mouse (except in poliomyelitis), and the route of inoculation intracerebral or, occasionally, intraperitoneal. In poliomyelitis, the monkey has been used as the test animal,[7] but the multiplicity of the virus strains that cross react has frequently rendered this test impractical for routine diagnostic work. This test has also been used in yellow-fever surveys,[8] since mice are susceptible to the intracerebral inoculation of the yellow-fever virus.[9]

Intranasal inoculation of mixtures of influenza virus and serum into mice can be used as the basis of a neutralization test since the animals develop pulmonary consolidation upon exposure to the influenza virus after a suitable incubation period (usually seven days).[10] The neutralizing antibody of antivaccinial[11] and antiherpes[12, 13] serums can be estimated by the inoculation of suitable mixtures of virus and immune serum on the chorioallantoic membrane of the developing chick embryo and observing the reduction in the pox produced as compared to the number that develop after the inoculation of similar virus and normal serum mixtures.

Agglutination-Inhibition Test

The phenomenon whereby vital agents agglutinate red blood cells has become quite useful in investigative and diagnostic work. Originally it was described and used in the diagnosis of influenza[14, 15]; however, since that time its applicability to the study of a number of viruses has been demonstrated — namely, vaccinia,[16] variola,[17] mumps,[18, 19] scrub typhus[20] and various viruses affecting animals.[21-27] The agents vary in their capacity to agglutinate erythrocytes from different hosts; furthermore, not all individuals of a certain species provide cells that are agglutinable by a given virus.

Although the mechanism of agglutination is not understood, it clearly has no relation to the usual antigen-antibody reaction. Hirst[28] observed that infective and hemagglutinative materials in preparations containing influenza A and B virus were adsorbed from the fluid by erythrocytes and that, under proper conditions, they could be eluted from the red cells. He further showed that the erythrocytes from which the hemagglutinins had been removed were no longer aggregated by fresh homologous virus preparations. Burnet and his associates[21, 29] extended these observations by demonstrating that such treated cells, which were refractory to the homologous virus, were still agglutinable by other viruses.

The inhibition, by homologous antiserums, of agglutination of red cells by viral and rickettsial agents has been applied as a diagnostic procedure for influenza and the other agents that exhibit hemagglutination. The agglutinin is viral material, and the inhibitor is antibody. The antibody is titrated against a known amount of virus, and this is known as the agglutination-inhibition test.

The agglutination-inhibition test is entirely different in principle from the heterophil-antibody test described by Paul and Bunnell[30] in 1932 for the diagnosis of infectious mononucleosis. In the heterophil-antibody test, the serum of a patient with infectious mononucleosis is titrated for antibody that agglutinates the erythrocytes of sheep.

Cold-Hemagglutination Test

Serums of persons ill with certain diseases yield substances that agglutinate red blood cells at low temperatures but not at or above 37°C. These substances are in no way related to the viral hemagglutinins discussed in the section on the hemagglutination-inhibition test. Their chief interest and importance in the field of infectious diseases are the provision of a nonspecific but useful test for the diagnosis of primary atypical pneumonia. This phenomenon was first described by Landsteiner[31] in 1903, when he noted, while working with erythrocytes and serums of normal animals, the striking effect of low temperature, the disappearance of agglutination with a rise in temperature, the absorbability of the agglutinin in the cold and its release from the cells at higher temperature. Since that time, cold hemagglutinins have been described in various conditions, both normal and pathologic, with recent studies in primary atypical pneumonia yielding much information upon the technic of a test and the interpretation of the results obtained.[32-34]

Specific Serologic Tests for Bacterial Infections

The laboratory diagnosis of most bacterial infections is based primarily on the isolation and identification of the etiologic agent in pure culture. Rapid presumptive tests, by finding organisms of characteristic morphology and staining qualities, are of less value. However, serologic tests are available for a few bacterial diseases, and are most helpful when the causative agent is difficult or impossible to isolate and identify.

Salmonellosis

There are three main types of clinical manifestations of salmonella infection — namely, the enteric fevers, gastroenteritis and a localizing type

with foci in one or more organs accompanied by septicemia. There are many different species of salmonella causing these types of infections, but all are closely related antigenically. These relations are used as the main criteria for classification in the Kauffmann–White system,[35, 36] which now contains over 150 types. Among the enteric fevers, the classic type is typhoid fever, which is caused by *Salmonella typhosa* and is pathogenic only for man. Other salmonella organisms causing enteric fever but in a milder form are *S. paratyphi* (paratyphoid A), *S. schottmülleri* (paratyphoid B) and *S. hirschfeldii* (paratyphoid C). In this country, *S. typhimurium* is the organism most commonly isolated from patients with gastroenteritis, whereas *S. cholerasuis* is the most common organism found in the septicemic type of infection. Every salmonella strain is potentially capable of producing any of these three clinical types of infection.

Agglutinins can usually be demonstrated in the circulating blood of patients one or two weeks after onset of typhoid and enteric fever, septicemia or gastroenteritis of the more severe type. In mild diarrheas, the agglutination reaction may not become positive until after the symptoms have subsided, or it may remain negative.

In typhoid fever tests should be carried out for agglutinins against both O (granular or somatic) and H (floccular or flagellar) antigens of typhoid bacilli; however, O agglutinins appear to be of more significance since some cases fail to develop H agglutinins and since O agglutinins disappear more rapidly after vaccination. It is not necessary to test for the presence of the Vi antigen in the diagnosis of typhoid fever since these agglutinins are rarely present without H or O agglutinins and are frequently undetectable in serums of known typhoid cases.

Both O and H agglutination of typhoid bacilli in 1:80 or higher dilution are generally considered characteristic of typhoid infection unless vaccine has been administered recently. H agglutination in a 1:80 dilution or higher, but with little or no O, rarely occurs with serums of typhoid patients and is usually characteristic of typhoid carriers or those recently having received typhoid vaccine or, occasionally, those infected in the past but with no demonstrable carrier condition. O agglutination of 1:80 or higher, with little to no H, has been observed in serums of some typhoid cases; however, it is usually characteristic of infections with organisms antigenically related to *S. typhosa*. Agglutinations in dilutions no higher than 1:40 are regarded as "suggestive" and of questionable significance unless occurring during the first ten days of illness.

Vi agglutinins occur in the serum of 80 to 90 per cent of typhoid carriers and also in 5 to 10 per cent of persons with no evidence of infection — for example, after injections of typhoid-fever vaccine.[37, 38]

Because of the large number of salmonella species and the complexity of the antigenic structure, the diagnosis of other salmonella infections is based primarily upon the isolation of the etiologic agent, serologic tests being of much less value.

Tularemia

The test for specific agglutinins in the blood serum of patients with tularemia is one of the most reliable tests in the field of serology, as well as the most practical for the diagnosis of this disease. Specific antibodies rarely appear during the first week of the disease; however, they are almost always present by the end of the second week, rising sharply in the third week and reaching maximum titers by the fourth to the fifth week. Positive titers may persist for the remainder of the patient's life.

Significant titer limits are hard to set, but titers of 1:10 or 1:20 early in the disease should be followed up with subsequent periodic examinations. Vaccination results in the production of agglutinin titers of 1:10 to 1:160, usually for at least nine to eleven months.[39] There is frequent cross-agglutination between *Pasteurella tularensis* and the brucella organism.[40] Brucella absorbs homologous agglutinins from antitularensis serums. *Past. tularensis* is agglutinated in low titer by antimelitensis, antiabortus and antisuis serums but cannot absorb the homologous agglutinins from them. Therefore, serums from suspected cases of tularemia and brucellosis should be tested for agglutination of the organisms of both diseases, unless clinical manifestations point definitely to one or the other. Antibodies for a homologous organism are usually at a higher level than they are for heterologous agents. If a serum agglutinates all three brucella organisms to the same, or nearly the same, titer, agglutinin absorption tests should be carried out.

Brucellosis (Undulant Fever)

The brucella are rod-shaped bacteria (occasionally coccoid) living a strictly parasitic life and characteristically invading mesenchymal cells of various organs in man and animals. The present system of species classification is based on biochemical and dye-tolerance tests and serologic analysis. The agglutinin absorption reveals the existence of two main antigenic groups: one including the abortus and suis species, and the other the melitensis species. The three species have a broad range of pathogenicity, including man and various naturally infected animals. The pathways of infection accepted as the most frequent in man are the intestinal and percutaneous with the reticuloendothelial system being chiefly involved in a granulomatous process. Human infections present an extremely diversified clinical picture. In the acute stage, the symptoms are similar to those of many other infectious diseases; in the chronic stage, they are often multiple, vague and difficult to evaluate.

Hence, the physician must rely greatly upon the laboratory to substantiate or render unlikely clinical impressions.

The main laboratory procedures used for the diagnosis of brucellosis are culture of organism from blood or other tissues, the agglutination test, the opsonocytophagic test and the skin test. Isolation of the causative organism is the only positive proof in the diagnosis of infection; however, this is difficult, since organisms are few and irregularly present in the blood and other body fluids. Of the other three tests available, the agglutination test is probably the most widely used. The opsonocytophagic test is involved and demands great precision; furthermore, it must be performed shortly after the blood is drawn, which renders it impracticable for the practitioner caring for patients in the home. The skin test is of limited value since it merely connotes previous contact and sensitization when positive. Furthermore, it should be remembered that antigenic material capable of stimulating the production of agglutinins and opsonins is injected during the skin test: hence, all other antibody tests should be completed before a skin test is done.

Although most widely used, the agglutination test has its limitations because of biologic variations due to the organism and to the host and because of discrepancies arising in the performance of the test. Agglutinins are usually present by the end of the second week and may reach titers eventually as high as 1:10,240. Titers may show an irregular course, especially in chronic cases. Occasionally, agglutinins may fail to appear even in culturally proved cases or may disappear after once being present in cases in which the pathologic process continues. The possibility of a prozone reaction must be kept in mind,[41-43] along with "blocking-type" antibodies.[43] On the other hand, a positive titer is not necessarily indicative of active disease if symptoms are not present; however, it may presage active, severe infection[41] or a subclinical infection that may later become severe.[44] Anamnestic or cross-agglutinative reactions may occur in the presence of other infections or vaccinations, especially with *Past. tularensis*[40] and *Vibrio cholera*.[45-47] These agglutinins for brucella after vaccination against cholera may persist for two or more years.[48]

There is no "diagnostic" agglutination titer in brucellosis. Titers of 1:80 to 1:320 and above have been suggested as presumptive evidence of the disease in the presence of symptoms. A rising titer during the course of an undiagnosed febrile illness is of some significance. A fluctuating titer, which correlates with the recrudescence and remission of symptoms, may suggest an active infection. Vaccine therapy, even one injection, renders the test meaningless for months.

Tests for Spirochetal Infections

Among this group of organisms, the borrelia, the treponema, and the leptospira are considered pathogenic to man. The borrelia include organisms causing Vincent's angina and relapsing fever, the treponema those causing syphilis, bejel, yaws and pinta, and the leptospira those causing hemorrhagic jaundice or Weil's disease. Laboratory methods in the diagnoses of these infections usually consist of finding the etiologic agent in the blood or lesion smears from an infected person or in the blood or organs of animals inoculated with infectious material. Serologic tests have been used extensively in the diagnosis of syphilis, but only moderately so in hemorrhagic jaundice. A serologic test has been described for relapsing fever,[49] but it has not been used widely.

Syphilis

The quantitative titer of syphilitic serum may be determined by several methods. The smallest amount of antigen required for a positive reaction can be measured, the least amount of complement necessary to produce fixation can be determined, or the serum can be diluted until it ceases to give a positive complement-fixation or flocculation reaction.[50] The last-named technic is the one most widely used. The serologic reaction is performed with serial dilutions of serum, the reagin titer being the highest dilution of serum giving a positive result.

Quantitative serologic tests for syphilis have many uses and values. A sharply rising reagin titer is usually found in a very recently acquired infection, a stationary titer indicates a syphilitic infection of some duration, and a falling titer without treatment usually represents a false-positive reaction.[51, 52] The last type of reactions, which are usually of low titer, may persist for several weeks, and mistaken diagnoses of primary syphilis may easily be made in these cases. Therefore, it is important to do serial quantitative tests for syphilis in the presence of genital lesions or skin lesions that are dark-field negative in early syphilis and whenever there is no corroborative evidence other than a positive qualitative test in late syphilis.

A child born of syphilitic parents should have quantitative tests at regular intervals to determine the disappearance of the maternal reagin, which is often transmitted to the child through the placenta, or the gradual appearance of his own antibodies. Approximately 15 per cent of positive cord tests revert to negative,[53] and about the same number of negative tests become positive when repeated later in infancy. Comparative studies of reagin titer of mother and child might be performed, since almost invariably the transmitted reagin in the child is equal to or less than that in the mother.[54] Therefore, a reagin titer in the infant well above that in the mother should be evidence of syphilis in the child. However, the finding of a quantitative titer in a child less than that of its mother does not exclude the possibility of congenital syphilis.

Just as in the initial syphilitic infection, there is frequently a rise of reagin titer in early relapsing syphilis. Quantitative tests can be particularly helpful when recurring syphilides are atypical or when there is a serologic reversal in patients considered adequately treated. However, it must be remembered that early cutaneous relapse is not always associated with a rise in serum reagin titer; some patients may even show a negative reaction.[55] Late gummatous lesions, isolated ocular relapse and neurorelapse may cause no changes in serum titer.

Quantitative tests are one of the simplest aids in the detection of biologic false-positive reactions. A rapidly falling or fluctuating titer in the absence of treatment is evidence of the presence of nonsyphilitic reagin.[52] False-positive reactions usually seen in normal adults are quite low; however, in children with febrile illness, the false-positive titer may be quite high. Repeated quantitative tests are necessary, for rising titers may be caused by an intercurrent illness rather than an actual increase of syphilitic reagin itself.[55]

When there is strong clinical evidence of syphilis but a negative or doubtful qualitative test, quantitative testing is indicated to rule out the prozone phenomenon. The incidence of serums that show the prozone phenomenon in flocculation tests is very low — approximately 1 per thousand[56]; therefore, quantitative testing of all doubtful or negative reactions is wasteful.

In modern rapid methods of treatment, the trend of the reagin titer is important in determining the immediate results of therapy, for rapid treatment schedules are completed long before the serologic reactions have had time to reverse themselves.[57]

Although low titers are found most often in late syphilis and high titers in early cases, there is so much variation that routine quantitative reactions are of little value in differentiating early from late syphilis.

Leptospirosis (Spirochetal Jaundice or Weil's Disease)

Several strains of leptospira have been isolated from human cases with the more important being *L. icterohemorrhagiae*, *L. canicola*, *L. hebdomadis*, *L. autumnalis* and *L. grippotyphosa*. *L. icterohemorrhagiae* is the classic cause of Weil's disease. The serologic relation of these organisms are not quite clear as yet, and there is some doubt concerning their classification as distinct species. However, they are said to be serologically distinct from each other but with considerable overlapping in their antigenic structure.

The agglutination test has been used with good results in the diagnosis of this infection. Agglutinins usually appear by the end of the first week of illness, reaching their maximum after four to seven weeks.[58] They gradually fall thereafter, but may persist for years in low dilutions.[59, 60] By the end of the first week of illness, the titer should be at least 1:20; during the second week it rises to and beyond 1:1,000, at a later stage it may go as high as 1:50,000. Patients showing titers of less than 1:100 should be re-examined for a rise in titer. A titer of 1:1,000 with suggestive clinical findings is considered by some as indicative of a present or recent infection.[61]

Tests for Viral Infections

Serologic methods have been used extensively in viral work and have increased the rapidly growing knowledge of viral agents. Most of the basic technics have been borrowed from bacteriology and immunology, but these generally have been modified because of difficulties encountered in obtaining appreciable quantities of pure viral antigens.

Virus Encephalitides

Virus encephalitides are usually divided into three main groups: encephalitis caused by viruses not ordinarily encephalitogenic, suspected primary viral encephalitic infections and primary viral encephalitic infections. Virus encephalitides caused by ordinarily nonencephalitogenic viruses can result from infection with herpes simplex, measles, lymphogranuloma venereum, mumps and infectious mononucleosis, which is probably due to a virus. With this group secondary or post-infectious encephalitides can be classified even though a viral etiology has not as yet been established. These encephalitides occur shortly after infection with measles, mumps, influenza, varicella, variola, infectious hepatitis and dengue and yellow fever, or after vaccination against smallpox (vaccinia) and rabies.

Suspected primary virus encephalitides consist of a group of newly discovered viruses that are neurotropic in laboratory animals. Furthermore, antibodies against these viruses have been found in the blood of man, but a clear-cut clinical encephalitic type of infection in man has yet to be seen. These viruses are: West Nile; Bwamba fever; Semliki forest; Bunyamwera; Hammon–Reeves, California; and Ilheus encephalitis. The first two have been recovered from the blood of man, and the remainder from mosquitoes only. Other suspected primary virus encephalitides are encephalitis lethargica (von Economo's disease), acute hemorrhagic meningoencephalitis, encephalomyocarditis and acute disseminated encephalomyelitis; however, their virus etiology has not as yet been established.

The primary virus encephalitides are St. Louis, eastern equine, western equine, Venezuelan equine, Japanese B and Russian Far East (tick-borne, spring-summer) encephalitis, all of which are of the epidemic type. The remainder of the primary group are nonepidemic and consist of lymphocytic choriomeningitis, pseudolymphocytic choriomeningitis, swineherd's disease, louping-ill, rabies and Sabin B virus.

This discussion is limited to the primary virus encephalitides that are known to exist in the United States and for which diagnostic serologic tests are rather readily available. Serologic tests for viruses causing encephalitis, although ordinarily not encephalitogenic, are discussed below along with the entire pathologic process, if such tests are available. The suspected primary virus encephalitides are not discussed, since their significance in human infections is not known at present or serologic tests are not readily available.

(To be concluded)

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 36511

PRESENTATION OF CASE

First admission. A sixty-two-year-old woman was admitted to the hospital for study.

Seven months before entry the patient noted the onset of aching pain in the middle and upper back. The pain was aggravated by movement of any sort and moderately relieved by a heat lamp. This symptom gradually disappeared over a period of three months but was followed by similar pain first in the right shoulder and then in the left shoulder; later, both wrists and hands became painful. The patient thought that there had been swelling of the fingers and wrist joints and that the symptoms were worse in damp weather. There was very definite morning stiffness and aching. There had been no evidence of fever, but she had experienced occasional chilly sensations. During and prior to the present illness she had been aware of increased nervousness and also had noted vasomotor instability, flushing, sweating of the hands and easy fatigue.

She had had scarlet fever as a child, and a left mastoidectomy, an appendectomy and cholecystectomy, thirty-eight, twenty-nine and sixteen years respectively before admission. Bilateral femoral-vein ligations were performed seven years previously for thrombophlebitis. Many disturbing factors regarding the patient's domestic life had been present for many years. Moderate dyspnea with exertion had been present for seven years. One sister had rheumatoid arthritis.

On physical examination no definite lymph-node enlargement was noted. The chest was clear and the heart was normal. There was some fusiform swelling involving the left wrist and proximal phalangeal joints of the fingers on the left with limited flexion and extension of the wrist. There was 90° abduction in the right shoulder and 60° on the left with pain. Motion of the neck was somewhat limited because of pain.

The temperature, pulse and respirations were normal. The blood pressure was 130 systolic, 60 diastolic.

The urine had a specific gravity of 1.022 and gave a + test for albumin; the sediment contained occasional granular casts. Examination of the blood disclosed a hemoglobin of 9.7 gm. and a white-cell count of 10,000, with 62 per cent neutrophils, 22 per cent lymphocytes, 9 per cent monocytes, 6 per cent eosinophils and 1 per cent basophils. The red-cell count after a transfusion was 3,750,000. The sedimentation rate was 0.80 mm. per minute, and the hematocrit 38 per cent. A blood Hinton test was negative. X-ray films of the hands showed slight generalized osteoporosis. There was narrowing and irregularity of the distal interphalangeal joints of the fifth fingers of both hands, more marked on the right, and cystic changes in the underlying bone. The other distal interphalangeal joints showed slight hypertrophic changes. There was generalized osteoporosis of the right shoulder, but the joint surfaces were smooth.

In the hospital the patient was placed on a regimen of limited activity, hot baths and packs, acetylsalicylic acid, ferrous sulfate, vitamins and active exercises for the joints. During the period of hospitalization she was given four 500-cc. blood transfusions. The symptoms diminished markedly, there was increased ability to move the shoulders, and except for morning stiffness she was fairly comfortable. She remained afebrile while in the hospital and was discharged after a month. She was given a detailed regimen similar to the one she had been on in the hospital to follow after discharge.

Second admission (three months later). In the interval she had conscientiously followed the regimen given her. Two weeks after discharge she suddenly developed swelling, tenderness and stiffness of the wrists and fingers. Later, there was similar involvement of the hips, shoulders and elbows, and pain in the region of the sacrum. These symptoms became progressively worse although there were brief periods of improvement.

On physical examination there appeared to be slight weakness of the palatal muscles on the left. There were 4-mm., hard, freely movable, bilateral supraclavicular lymph nodes and a right epitrochlear lymph node measuring 1 cm. in diameter. The chest was clear, and the heart was not enlarged. There was a Grade II, blowing, systolic murmur, heard over the whole precordium but best at the apex. The liver edge was felt two fingerbreadths below the costal margin. Motions of the neck, shoulders, elbows, wrists, fingers and knees were limited. There were bilateral knee-joint effusions. In addition, both wrists were swollen, hot and tender. Muscle wasting was now definite. There was a tender

subcutaneous nodule 1.5 cm. in diameter, apparently attached to the sacrum.

The temperature, pulse and respirations were normal, and the blood pressure 118 systolic, 58 diastolic.

The urine had a specific gravity of 1.002, and the sediment contained occasional red cells and 8 white cells per high-power field. Blood studies were essentially the same as at the time of the previous admission, and the nonprotein nitrogen was 20 mg. per 100 cc. The sedimentation rate was 1.39 mm. per minute, and the hematocrit 34.5 per cent. A urine examination done following a febrile transfusion reaction revealed a ++ test for albumin and a sediment containing occasional coarsely granular casts, rare hyaline casts and red cells. Four days later a urine examination was again negative. Roentgenograms of the various joints showed definite progression characterized by demineralization and reduction of joint spacing. There were intermittent febrile episodes lasting several days to a week with a maximum temperature of 102°F. The marked joint swelling and muscle wasting progressed. The patient had severe febrile reactions to the transfusions given, during one of which the temperature was 106.4°F. by rectum and for which she had amnesia. During the next four weeks the temperature gradually returned to normal, and she was subsequently afebrile. A positive remission of symptoms ensued, and she was able to walk about at the time she was discharged five months after entry.

Third admission (about three and a half months later). About a month following discharge the patient noticed that the ankles became swollen toward evening. This was painless, in contrast to previous episodes of swelling. Within a week swelling was marked, extended up to the thighs and was present constantly although more marked in the evening. There were no signs of inflammation. During the month prior to admission, the patient was kept on bed rest, with some decrease in the swelling. She had gained 7 pounds since the previous admission and had noted rather marked fatigue, weakness and slight dyspnea.

Physical examination showed a slightly dyspneic, pale woman. There were palpable cervical, epitrochlear, axillary, inguinal and femoral lymph nodes, some of which were tender. Moist rales were heard at the end of inspiration at the left base, and the heart appeared to be moderately enlarged. The liver edge was just palpable, and there was marked pitting edema of the lower extremities extending up to the lower thoracic region posteriorly and the inguinal ligaments anteriorly. There was slight edema of the eyelids and face. There was no pain on motion of any of the joints except for the temporomandibular joints. Other joints showed slight to no limitation of motion.

The temperature, pulse and respirations were normal. The blood pressure was 116 systolic, 52 diastolic.

The urine examinations done during this admission all gave ++ to ++++ tests for albumin, and the sediments contained many granular and hyaline casts, an occasional red cell and fairly numerous white cells, with frequent clumps. During the urine-concentration test the maximum specific gravity was 1.012, and the highest specific gravity recorded on any of the urinalyses was 1.014. Examination of the blood revealed a hemoglobin of 10.7 gm. and a white-cell count of 9100, with 51 per cent neutrophils, 31 per cent lymphocytes, 6 per cent monocytes, 11 per cent eosinophils and 1 per cent basophils. The sedimentation rate was 2.0 mm. per minute, and the hematocrit 34.5 per cent. The nonprotein nitrogen was 26 mg., the albumin 1.89 gm., and the globulin 1.99 gm. per 100 cc.; the sodium was 138.6 milliequiv., and the potassium 5.3 milliequiv. per liter. A cephalin-flocculation test was +++ in forty-eight hours. A phenolsulfonphthalein test revealed 20 per cent excretion of the dye in 15 minutes, 5 per cent in 30 minutes, 10 per cent in 1 hour and 10 per cent in 2 hours. A Congo-red test demonstrated 35 per cent retention of the dye in the serum after 1 hour. The twenty-four-hour urinary excretion of protein was 22.4 gm. An electrocardiogram was normal.

Although the patient complained little of the joints a conservative regimen for arthritis was continued. In addition she was placed on a low-sodium diet with fluid intake limited to 1500 cc., and she was given Mercuhydrin. The peripheral edema responded to this therapy, and she was discharged improved six weeks later.

Fourth, fifth and sixth admissions (four, five and ten months later, respectively). The patient was readmitted because of coughing, nausea, vomiting, tremor, weakness, recurrence of peripheral edema and mental confusion. She had few complaints relative to the joints during this period. She continued to be anemic and required repeated transfusions. The blood pressure was 142 systolic, 65 diastolic during the fourth admission, 76 systolic, 50 diastolic during the fifth, and 62 systolic, 30 diastolic during the sixth. On various examinations, the urine had specific gravities ranging around 1.010, with a maximum of 1.020, and gave ++ to ++++ tests for albumin, and the sediments contained 15 to 100 white cells and a few red cells per high-power field. The nonprotein nitrogen ranged from 78 to 150 mg. per 100 cc., usually being in the neighborhood of the higher levels. A second Congo-red test was reported as showing 45 per cent retention in the serum. For two weeks during the sixth admission, the patient was moribund and had severe acidotic breathing. On one occasion while she was comatose the sodium was 162.6 milliequiv., the chloride 119 milliequiv., the potassium 5.7 milliequiv.

and the carbon dioxide 7.7 milliequiv. per liter. The hemoglobin was 9 gm. She was given four transfusions of 500 cc. of whole blood. She again improved and was discharged after about two and a half months.

Final admission (about two and a half months later). In the interval the patient had only mild bouts of arthralgia and was able to be up and around from time to time. Two weeks before entry she had a rapid gain in weight, swelling of the abdomen and frequent epistaxes.

On physical examination there was distention of the neck veins without pulsation. The heart had a normal sinus rhythm and a Grade II apical systolic murmur but no rub. The liver edge was one finger-breadth below the costal margin, and there was free fluid in the abdomen. The spleen was not felt. There was moderate deformity of the finger joints but no evidence of active disease.

The temperature, pulse and respirations were normal. The blood pressure was 90 systolic, 60 diastolic.

Urine and blood findings were essentially the same as those found during the three previous admissions. The sodium was 120.8 milliequiv., the chloride 88 milliequiv., the potassium 6.3 milliequiv., and the carbon dioxide 14.8 milliequiv. per liter.

On the second hospital day the patient had another febrile transfusion reaction followed by nausea, constant retching and some dyspnea. On the following day she was comatose and had slow, irregular respirations, weak pulse rate and a steadily falling blood pressure. Later the same day she died.

Differential Diagnosis

Dr. Jacob Lerman*: This is a long problem; the patient was sick for approximately three years and had seven hospital admissions in that length of time. Superficially the picture was very characteristic of rheumatoid arthritis, with perhaps some hypertrophic arthritis. I should like to review the significant findings. There was a history of scarlet fever and mastoiditis, an anemia, a well described arthritis, a normal blood pressure, a + test for albumin, an occasional granular cast and some cells in the urine, and 6 per cent eosinophils in the blood smear. These seem to be the important findings. An unusual feature was the febrile reaction to the transfusion, which raises the question of a hemolytic crisis. Even though the blood is typed carefully, there are several rare types of agglutinins that may not be detected and may produce hemolysis of red cells and an acute reaction. The description, however, does not fit a lower-nephron nephrosis. All I can say is that there was some type of transfusion reaction, probably not associated with hemolysis but possibly associated with rare agglutinins.

Dr. John W. Zeller: We later gave the patient a large dose of aspirin and 50 mg. of pyribenzamine before each transfusion, and that treatment apparently helped. There were no more severe reactions, and subsequently she was able to tolerate transfusions without any previous medication.

Dr. Walter Bauer: There was no anuria or marked oliguria following even the most severe of the transfusion reactions.

Dr. Zeller: She had a normal nonprotein nitrogen the day following the most severe reaction.

Dr. Lerman: Then I may assume that there was no blocking of the tubules. I have been interested in transfusion reactions and believe that cold blood will produce reactions but I have never proved the point. In some of the patients who are very sick, cold blood as it comes from the icebox, probably about 10°C., can produce reactions — fever, nausea and vomiting.

Dr. Bauer: We have a rule here that blood must be warmed before being used.

Dr. Lerman: On the second admission, there was weakness of the palatal muscles, which I cannot interpret, lymph-node enlargement, a large liver, an increase in the size of the joints, muscular wasting and a tender subcutaneous nodule, which was probably no different from the nodes that one finds in rheumatoid arthritis. There was no fever. The low specific gravity of the urine and the few red cells in the sediment are important. There was no evidence of nitrogen retention. There was progression of the arthritis and finally a remission.

On the third admission, there was evidence of more renal damage and of cardiac failure. There was slight dyspnea, edema and some rales at the bases but certainly not enough to explain the edema, which must be accounted for by the serum protein of 3.9 gm., with a ratio of less than 1. There was some decrease in phenolsulfonphthalein function. Amyloid disease was suggested by a Congo-red test showing 35 per cent retention, and liver involvement by the positive cephalin-flocculation test. Perhaps the tender lymph nodes might be considered evidence of amyloid involvement of the lymph nodes.

In the final admissions a striking finding was the fall in blood pressure.

Dr. Bauer: On the next to the last admission the patient was moribund; in fact we even obtained permission for a post-mortem examination, thinking it would be done within twenty-four hours. However, with repeated transfusions she made a good recovery and was again reasonably comfortable for another three months.

Dr. Lerman: I cannot explain the falling blood pressure on the basis of cardiac failure. There was nothing in the protocol to suggest that cardiac failure was progressive or severe. The drop in blood pressure may have been due to some other factor such as adrenal failure. I shall discuss this a little later.

A sodium value of 163 milliequiv. per liter is a bizarre finding that I cannot explain unless she was receiving sodium and was oliguric. A Congo-red

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test showing 45 per cent retention at that time puts me on doubtful ground regarding the diagnosis of amyloid disease. The low sodium, the low chloride, the high potassium and the acidosis during the last admission are consistent with renal failure and also with Addison's disease.

May we see the x-ray films?

DR. STANLEY M. WYMAN: The films of the original examination of the hands and right shoulder show rather marked osteoporosis of the ends of the long bones. There is joint-space narrowing, minimal in the interphalangeal joints proximally but more pronounced in the distal joints, and some degenerative changes particularly in the right fifth finger. There seems to be some soft-tissue swelling.

DR. BAUER: What about the other films?

DR. WYMAN: Not very striking, Dr. Bauer. The right shoulder does show some loss of bone in the posterior aspect of the head of the humerus, but the joints otherwise appear preserved. There is considerable osteoporosis.

The films taken about six months later demonstrate an increase in osteoporosis, considerable narrowing of the proximal interphalangeal joints and very definite soft-tissue swelling about the joints quite consistent with rheumatoid changes. We have chest films, but I do not think they are contributory.

DR. LERMAN: The x-ray films merely confirm our clinical impression of rheumatoid arthritis in addition to some hypertrophic changes in the fingertips.

There are several diagnoses that I have to consider. The first question is whether this patient had chronic glomerulonephritis. There seems to be a good deal of evidence to support this diagnosis. There was a history of scarlet fever and other infections in the past; she had evidence of renal damage under stress conditions; anemia appeared early in the course, with little evidence of any disease other than rheumatoid arthritis. Then she developed a nephrotic stage lasting for several months, with edema and marked albuminuria, and finally uremia. All these findings are frequently seen in the course of chronic glomerulonephritis.

DR. BAUER: Is it not unusual to have glomerulonephritis beginning at this age?

DR. LERMAN: There may have been episodes in the past from which the patient recovered. In chronic glomerulonephritis there is a great tendency to hemorrhage. If hemorrhage occurred in the adrenals, it would account for the sudden drop in blood pressure and for the electrolyte picture. This is only conjecture. If she had had hypertension in the past, it would be stronger evidence for the diagnosis of chronic glomerulonephritis, but the absence of hypertension does not rule it out.

There is no doubt that this patient had amyloid disease. She had a large liver, evidence of liver damage as indicated by a positive cephalin-flocculation test and a positive Congo-red test, and rheumatoid arthritis. Patients with rheumatoid arthritis are prone to amyloid disease. However, amyloid would not explain the whole renal picture. It may account for that portion that we call the nephrotic stage — the marked albuminuria, the low serum protein and the marked edema without renal damage. Occasionally, patients with long-standing amyloidosis develop renal failure. Also amyloid deposits may appear in the adrenal gland, to cause Addison's disease. This would account for the final chemical determinations.

Another diagnosis I shall consider is periarteritis nodosa. There was no obvious etiology for the periarteritis unless one can assume that transfusion reactions are a mechanism for its development. I have never heard of this explanation. There are several things in favor of periarteritis nodosa. The eosinophilia, which persisted from the very first admission, and the renal involvement that often leads to renal failure are common in periarteritis nodosa. Against the diagnosis of periarteritis nodosa are the absence of nerve palsies, the absence of febrile episodes that cannot be explained on the basis of joint symptoms only, the absence of pain in parts of the body other than the joints, the absence of leukocytosis, the absence of typical periarteritis nodules and the long periods of remission, which would be somewhat unusual. Usually, the course of the disease is progressive and downhill.

DR. BAUER: What about the absence of hypertension?

DR. LERMAN: This may occur or may be absent. Periarteritis could also produce adrenal damage to cause adrenal failure.

A final diagnosis we have to consider is lupus erythematosus. There is not enough evidence in the protocol pointing to the skin and other organs to suggest that this ought to be entertained seriously.

DR. BAUER: What if I told you that Dr. Hugh J. Chaplin, who is a very good observer, had noted a couple of lupus-erythematosus cells?

DR. LERMAN: I would be disturbed. However, there is not enough clinical evidence for me to consider lupus erythematosus. I am therefore forced to conclude that this patient had rheumatoid arthritis, a mild degree of hypertrophic arthritis and some congestive failure, but the main clinical picture was that of chronic glomerulonephritis with amyloidosis, or possibly periarteritis nodosa. It is very hard to choose between periarteritis nodosa and chronic glomerulonephritis. I merely put the emphasis on chronic glomerulonephritis.

DR. BAUER: This patient was followed by us for approximately three years. We, too, made a diagnosis of rheumatoid arthritis. There was never any doubt in our minds about that diagnosis until Dr. Chaplin reported the presence of lupus erythematosus cells in one of the recent blood smears. Our diagnoses at the time of the various discharges

in addition to rheumatoid arthritis were ?nephrosis, probably amyloid disease, amyloid nephrosis, and finally chronic glomerulonephritis.

This patient has taught us a good deal. During the past twenty years we have observed 8 or 10 patients with similar skeletal symptoms and articular findings. They have caused us to ask the question, What is rheumatoid arthritis? The case under discussion brings forth certain speculations on my part. I wish to emphasize that they are mere speculations. Dr. Mallory may or may not agree with me — and it is very likely that he will disagree with me. If enough blood vessels are examined in the average case of rheumatoid arthritis one stands a good chance of finding some degree of vasculitis. In this case, I shall raise the following questions: Are we dealing with anything more than rheumatoid arthritis with extensive vasculitis? What are periarteritis nodosa, lupus erythematosus disseminatus, dermatomyositis and scleroderma? Are they all examples of different grades of localizing vasculitis that have been classified by some as distinct pathologic entities? Are they related? If they are, should one consider them as entities? Until the needed information is at hand it is perhaps best to continue to separate them; however, we should bear the other possibility in mind.

These x-ray changes should not disturb one. I have seen a patient in this hospital who, following her first attack of lupus erythematosus disseminatus, exhibited fusion and considerable destruction of the bones of one wrist. This patient experienced a fifteen-year remission; the second and last attack began with a typical facial erythematous rash, with subsequent dissemination and death.

Clinical Diagnoses

Rheumatoid arthritis, with secondary amyloidosis.
Uremia.
?Glomerulonephritis.

Dr. Lerman's Diagnoses

Chronic glomerulonephritis
Amyloidosis.
Rheumatoid arthritis.
?Periarteritis nodosa.
Congestive heart failure.

Anatomical Diagnoses

Polyarteritis and vasculitis, generalized, severe.
Acute and chronic glomerulitis.
Myocarditis, severe.
Rheumatoid arthritis.
Amyloidosis of kidney.

Pathological Discussion

Dr. Tracy B. Mallory: This is another of the cases that refuse to fit into any exact pigeonhole. The gross findings at autopsy were very slight. The heart was of normal size and showed a little calcification of the annulus of the aortic and mitral valves, but the valve leaflets were grossly normal. There was no polyserositis and no inflammation of the pericardium, pleura or peritoneum. The liver was normal in size, as was the spleen. The kidneys were definitely shrunken and atrophic, weighing together just under 150 gm. The joints showed very little grossly. There was no pannus and no destruction of the cartilage, and the synovia was a little darker and browner than normal. There were a few fibroids in the uterus.

Figure 1.

In contrast to the very meager gross findings, the microscopical findings were extensive and extraordinary. Every organ of the body of which we had more than one or two sections showed some degree of vascular involvement, and this vasculitis was not limited to the arteries but was present in veins and also in many lymphatics (Fig. 1), which I have not seen before. Besides the vascular lesions there were interstitial lesions of the myocardium that to many eyes were classic for rheumatic myocarditis — Aschoff nodules (Fig. 2). When it comes

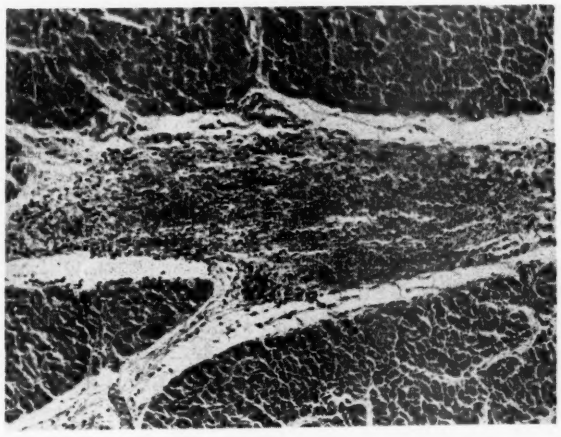

Figure 2.

to the kidneys, I am at a complete loss. Stains for amyloid showed amyloid in many glomerular tufts. None was found anywhere else in the body. There was also marked evidence of inflammation and proliferating crescent cells such as one finds in glomerulonephritis and I would not suppose could occur in amyloid nephritis. I think one must say that there was glomerulitis. Whether glomerulitis antedated the amyloid disease or not I cannot say. There was also an unusual degree of interstitial infiltration.

I have quite a few pictures I can show to illustrate some of the lesions. This first is from the pylorus and demonstrates a vascular area with a granulomatous reaction completely surrounding it. There is no necrosis of the vessel wall such as has been described in the classic lesion of periarteritis nodosa. On the other hand, lesions of this type are frequently found in cases of periarteritis that are typical in another area. This is the lesion in the heart, showing a focal granuloma with numerous giant cells. There is a vessel rather on the edge of the area that would certainly suggest periarteritis and one would think of some peculiar granulomatous process.

DR. BAUER: Were you able to demonstrate any fibrinoid areas?

DR. MALLORY: There was some fibrinoid change in the wall of some of the vessels and very marked periarterial granuloma.

This is a vessel from the spleen, showing a slight granulomatous reaction about the central artery and malpighian corpuscles and also some concentric fibrosis, a little reminiscent of what one sees in lupus.

DR. BAUER: Are you going to show us any lupus-erythematosus cells?

DR. MALLORY: I found none. This is a section of a small vein that shows in its lower wall a sharp focal granulomatous reaction. And here are lymphatics with reaction in the wall, and giant cells just to the side of the second one (Fig. 1).

There is a section of the synovia showing fibrous scarring and a great deal of hemosiderin. There seems to be no acute or progressive inflammation in the synovia at the time of death. This is consistent with a very acute stage of rheumatoid arthritis but is not particularly typical of it.

Here is a section of the kidneys, showing numerous hyalinized glomeruli, many of which did give an amyloid reaction, and here is a glomerulus showing crescent formation and acute glomerulitis. In the kidney very few vascular lesions were found. The high-power magnifications of most of these glomeruli show capillary obliteration.

I do not know what name to give this. So far as the autopsy is concerned I am unimpressed with rheumatoid arthritis. That is not saying that it did not exist, but it seemed like a minor element. Unquestionably, the renal lesion was the major and immediate cause of death. The diffuse vascular involvement was the most extensive I have seen but I cannot bring myself to say that it had very much to do with the symptomatology. We found, for instance, involvement of the blood vessels of nerves, but the patient had had no peripheral neuritis. We found marked involvement of the blood vessels in the skeletal muscle, but there had been no pain. We found involvement of vessels in the capsule of the adrenal, but there was no necrosis of the adrenal cortex and I could see no reason why the adrenal should not have been functioning reasonably well. I think this is one of the most severe myocarditides I have ever seen, and yet she had no heart failure.

DR. BAUER: There is an old saying, "live and learn." This case demonstrates very clearly how much remains to be learned. Previously, I referred to 8 or 10 cases that were not unlike this one. In 1 of these cases we were able to demonstrate the following: typical Aschoff bodies, characteristic lesions of periarteritis nodosa and changes consistent with those considered diagnostic of rheumatoid arthritis. The case under discussion illustrates all too well how much fun one has studying chronic disease, whether he is a clinician or a pathologist.

CASE 36512

PRESENTATION OF CASE

First admission. A fifty-eight-year-old man entered the hospital for an elective cholecystectomy because of epigastric pain.

The patient had experienced three attacks of severe, steady, nonradiating, midepigastric pain during the preceding year and a half. Each episode had required narcotics for relief. There were no other symptoms associated with the pain, and there was no jaundice, dark urine or light stools. No significant food intolerance had been noted. The Graham tests were reported to have shown a nonfunctioning gall bladder with stones. A gastrointestinal series, barium-ene na examination and electrocardiogram were reported as normal. The last episode had occurred during the preceding month.

Physical examination revealed a well developed and slightly obese man with no remarkable findings. The blood pressure was 170 systolic, 95 diastolic. The urine was normal. Examination of the blood disclosed a hemoglobin of 15.5 gm. and a white-cell count of 7500. The prothrombin time was 17 seconds (normal, 15 seconds), the total protein 6.7 mg. per 100 cc., and the nonprotein nitrogen 26 mg. per 100 cc. On the third hospital day a cholecystectomy and exploration of the common duct were done. A stone was found impacted in the cystic duct of a collapsed, scarred gall bladder. The common duct was somewhat constricted at the point where the cystic duct entered. Small stones and sludge were removed from the common duct. The common-

duct stricture and the not unusual ampulla of Vater were dilated up to 7 mm. A common-duct T tube was left in place. The pathological report was cholesterolosis and chronic cholecystitis with fibrosis of the cystic duct. A cholangiogram done on the ninth postoperative day revealed the dye to pass readily into the duodenum, with a common duct of normal size except for a slight narrowing just below the entrance of the tube. The tube was removed on the fourteenth day. The patient did well and was discharged home on the sixteenth day after operation.

Second admission (eleven months later). The patient was asymptomatic until ten months following operation, when epigastric pain similar to that preoperatively returned along with anorexia, nausea and daily eructations. He suffered mild distress of this nature for about six weeks. Then the pain became acutely severe, and was associated for the first time with jaundice, dark urine, light stools, shaking chills and a maximum temperature of 102°F.

Except for slight icterus and a palpable tender liver edge four fingerbreadths below the costal margin the physical examination was negative.

The white-cell count was 11,700. The serum bilirubin was 5.8 mg. direct, 7.8 mg. total per 100 cc., the serum amylase 29 mg. per 100 cc., and the cephalin-flocculation test negative.

The symptoms rapidly subsided with conservative therapy, and after five days he was discharged home asymptomatic, although the urine was still dark at times and the scleras questionably icteric.

Third admission (eighteen days later). Eight days prior to admission, the pain returned along with a chill. A temperature as high as 100°F. persisted along with the epigastric pain extending into the right upper quadrant. He was given chloramphenicol (Chloromycetin), 2.0 gm. daily, for three days. The pain and fever subsided for several days, only to return on the day before entry.

Physical examination again revealed a slight icterus. Except for slight discomfort on deep palpation in the right upper quadrant, the abdominal examination was not remarkable.

The temperature was 99.6°F., the pulse 80, and the respirations 18. The blood pressure was 128 systolic, 72 diastolic.

Examination of the blood showed a hemoglobin of 14.0 gm. and a white-cell count of 23,200, with 86 per cent neutrophils. The urine was normal except for a + test for bile and a urobilinogen positive at 1:25 dilution. The prothrombin time was 17 seconds (normal, 18 seconds). The serum bilirubin was 1.4 mg. direct, 2.2 mg. total per 100 cc. Duodenal drainage showed a sediment of bilirubin and cholesterol crystals without cells.

On the second hospital day an operation was performed.

Differential Diagnosis

Dr. Richard H. Sweet*: On the surface this looks like a perfectly straightforward case of gallstones. There were attacks of pain and a positive Graham test showing a nonfunctioning gall bladder. The collapsed, scarred gall bladder seems to indicate that this was a long-standing process. The one thing in this history that seemed to be exceedingly unusual was the constriction of the common duct where the cystic duct entered; that is unusual without symptoms because there had been nothing previously to suggest stones in the common duct. Of course, stones may sometimes exist in the common duct without the presence of jaundice. The stricture in the common duct due to gallstones suggests that possibly there was an incipient neoplastic process although strictures of that region are more likely to be due to surgical trauma or ulceration from calculi.

"A cholangiogram done on the ninth postoperative day revealed the dye to pass readily into the duodenum, with a common duct of normal size except for a slight narrowing just below the entrance of the tube." I do not believe I attach too much significance to that because the stricture as described was in the region of the cystic duct. I have to make the assumption that the T tube was inserted in the common duct somewhat below the level of the cystic duct, which is the most frequent place to put it. Now, if there was another stricture or a narrowing of the lower part, I do not believe this x-ray shadow meant very much unless it represented a foreign body — a piece of stone or something of that sort.

Dr. Tracy B. Mallory: I believe Dr. Wyman has another cholangiogram, which is somewhat different from that.

Dr. Sweet: May we see that, Dr. Wyman? What I get out of the typewritten report is that there were two areas of narrowing in the common duct, one observed at operation and the other observed postoperatively in the cholangiogram.

Dr. Stanley M. Wyman: The cholangiogram described in the protocol shows the hepatic radicles and the T tube entering the right radicle and extending down the common duct. The narrowing described at this point is a long, fusiform affair that is seen on all four films, and I do not know that I can make very much of it. There was no evidence of obstruction in the ampulla, which was of normal caliber.

Dr. Sweet: My assumption that the T tube was put in the common duct was wrong. The protocol says a common-duct T tube was left in place but it was apparently actually in the right hepatic duct.

Dr. Wyman: One branch is in the right hepatic and the other in the common duct.

*Visiting surgeon, Massachusetts General Hospital.

DR. CHESTER M. JONES: May I add one thing, Dr. Sweet: there was an impacted gallstone in the cystic duct right where it joined the common duct, and there was some deformity around the common duct.

DR. SWEET: Was it necessary to incise the common duct?

DR. GORDON A. DONALDSON: No; the stone was at the junction of the cystic and common ducts, and Dr. Arthur W. Allen removed the cystic duct flush with the common duct and drained the common duct just above the stricture.

DR. SWEET: Then my original impression, that there were two levels, was correct. It is a rather unusual place to put a common-duct drainage tube!

DR. DONALDSON: It was put in above at the second operation.

DR. SWEET: I wondered why it was put in at that level unless it was because of the stricture distal to that point. As we see from the cholangiogram, it was put into the hepatic duct.

The jaundice, chills and fever were evidence of an obstruction of the common duct with all the attendant symptoms, which indicates to me at least that the patient had an associated infection, a cholangitis that was the source of the pain. All that would be entirely consistent with the presence of a stone that might have been left in the common duct although the cholangiogram does not show it.

There is the statement that the patient still had jaundice because the urine was still dark and the scleras were icteric. That indicates that subsidence of this attack was not complete at the time he was discharged from the hospital, even though the obstruction may have let up.

It seems to me that the problem resolves itself into trying to decide whether or not there was anything unusual in the case. Why was this not just a case of gallstones with chronic cholecystitis and with a stone left in the common duct or the re-formation of stones? I have some inkling that it may not have been that because Dr. Allen did the operation and I doubt if he would have left a stone in the common duct. I do not know whether that is the proper reasoning, but at least I know enough about his ability to be sure that it would be exceedingly unlikely.

The question I should like to ask Dr. Jones is whether or not the mere finding of bilirubin and cholesterol crystals in the duodenal drainage is indicative of the presence of stones. In other words, cannot such a finding be present in deposits precipitated out of bile behind a stricture of any kind? Does it necessarily mean stones, or can it occur without stones?

DR. JONES: It may go with stasis behind a biliary obstruction particularly if there is infection, as there was here. In this case there was a tremendous amount of crystalline material — much more than is ordinarily found in an abnormal sediment. The high-power view was filled with calcium, bilirubin and cholesterol crystals that were almost microscopic conglomerates — they were microscopic stones really, and the chances are about three out of four that there would be stones along with this although there does not have to be.

DR. SWEET: I do not know what the comment "without cells" means. Does that mean without tumor cells?

DR. JONES: No; without a great many inflammatory cells — white cells as a rule and sometimes columnar epithelial cells too, but none of those were found. With an inflammatory process of any great degree one is likely to find cells.

DR. SWEET: It seems to me that there was very little in this case to suggest that there was anything unusual about it whatever with the single exception that at operation a stenosis was observed in the common duct without evidence of very much disturbance going on in the common duct at any time. In other words, the gallstone problem had been confined almost exclusively to the gall bladder at that time, and that made me wonder whether the narrowing might have had some basis other than a response to an inflammatory process or ulceration of a gallstone impacted in the cystic duct. I suspect that there may have been something else wrong with the common duct, possibly in the form of a neoplastic process, probably carcinoma, which is the only other thing I can think of.

DR. MALLORY: Let us ask Dr. Jones to tell us how the opinion ran up to this point.

DR. JONES: I think Dr. Allen and his group reasoned much as Dr. Sweet has, that they were dealing with stones in the common duct. On the morning of the operation, Dr. Donaldson and I discussed the possibility of cancer in addition to calculi.

The reason this patient was not operated upon during the second hospital admission was that Dr. Allen believed it was going to be a very difficult operative procedure. He had had a great deal of difficulty with the first operation. It was hoped that the patient might have had some gravel or a small stone that might be passed and that it might be possible to avoid operating. Our hands were forced after a second attack of jaundice, and the patient had to be explored. As it turned out it was a very difficult operation.

DR. DONALDSON: There was something peculiar about the first operation. The gall bladder was collapsed, and it was not greatly thickened. With an impacted stone it should have been distended. In addition there was the thickening of the common duct below the junction of the cystic duct with the common duct.

Clinical Diagnosis

Common-duct stone.

Dr. Sweet's Diagnoses

Common-duct stone.
Carcinoma, common bile duct.

Anatomical Diagnoses

Carcinoma, common bile duct.
Choledocholithiasis.

Pathological Discussion

Dr. Mallory: Would you describe the findings at operation?

Dr. Donaldson: Dr. Allen identified the gastrohepatic ligament readily enough and found a small abscess at the site where the T tube had been inserted. The opening was enlarged, and there was a considerable amount of grumous material, with some stone granules. Stones were found and in addition a considerable amount of granulomatous tissue exuded from the common duct — so much so that suspicions were aroused and Dr. Mallory came over and got some of it at the operating table.

Dr. Mallory: This material was sent to the laboratory and proved to be an epithelial polypoid tumor of which a considerable portion looked entirely benign but one part showed definitely malignant cytology. At this point the cholangiogram was once again repeated. We might see that, Dr. Wyman.

Dr. Wyman: This cholangiogram again shows the somewhat fusiform narrowing previously seen but perhaps not quite so strikingly. Down near the lower end of the T-tube limb there is a small constant filling defect most likely in the right wall perhaps 2 to 2.5 cm. above the ampulla.

Dr. Mallory: Following this Dr. Allen did a radical resection of the area, and cancer was found. When the dilated common duct was opened the ampulla of Vater was found to be normal, but around the mouth of the pancreatic duct was a slightly polypoid granular surface that consisted of carcinoma. The microscopical slides showed that the tumor had infiltrated through the wall of the common duct, but the regional lymph nodes were free from metastases. It seemed like an exceptionally early and favorable case for a possible cure.

Dr. Jones: I think I missed one opportunity to make the diagnosis before the second operation. The duodenal contents showed perfectly good evidence for a stone, and that seemed an explanation for the symptoms. We did not, however, send the specimen to the Cytology Laboratory for a Papanicolaou stain, which would probably have been positive, because at the time of operation a specimen had been sent and the same comment was made that was made on the microscopical section.

Dr. Donaldson: I would like to ask Dr. Sweet if he has ever seen segmental stricture of the common duct from chronic cholecystitis such as this might have been.

Dr. Sweet: No; only in cases in which there may be an impaction of a stone in the cystic duct close to the common duct, with enough inflammatory reaction localized to that point to cause a disturbance; otherwise they do not occur. That is what made me suspicious in this case that I was dealing with a carcinoma or something of that sort rather than just an inflammatory process.

Dr. Jones: That is exactly what was present — an impacted stone right at the junction of the cystic and common ducts. Dr. Mallory, can we take the time to ask Dr. Donaldson what the final anastomosis was?

Dr. Donaldson: The end of the pancreas was anastomosed to the end of the jejunum, and farther down the stomach was anastomosed to the side of the jejunum. It is almost a year since operation, and the patient is well.

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DEAN SHERWOOD LUCE

THE *Journal* takes great pride in paying its respects to that fellow of the Massachusetts Medical Society, who has achieved the greatest distinction in 1950. All honor to Dean Sherwood Luce, of Canton, chosen by the House of Delegates of the Ameri an Medical Association as the country's most eminent general practitioner of the year!

WHILE ROME BURNS

MOST physicians who watch the fires that are bursting into flame in the world today must wonder why more time and thought are not devoted to analysis of global problems by eminent social and medical scientists. Such participation is conspicuous in operational attacks, but conspicuously absent in the preventive approach. And yet if more anthropologists, historians, economists, geographers, epidemiologists and biostatisticians came out of their classrooms long enough, they might contribute to a rational solution of mankind's most pressing problems before the greatest world war actually bursts out.

Physicists and engineers, for all the brilliance of their Manhattan Project, fool few people, least of all those trained in medicine, into believing that anybody capable of inventing the atomic bomb is necessarily smart enough to come up with the right prescription for a sick world. The proposition is a *non sequitur*, and physicians who practice enough physical science to know its limitations as well as its potentialities, and enough social medicine to know how unscientific the social sciences are, ponder whether they have anything to offer during these precious moments while there is still time to think. If it is clear to the man in the street that the world is on fire, it is clear also to his doctor. Millions ask if the democracies are not fiddling while Rome burns, and expect their elected leaders and their doctors, lawyers, educators and clergymen to give an honest answer. They do not understand their procrastination. The question asked on all sides needs an answer. The smoldering is evident in every continent. The tempo of the scene is reminiscent of the dramatic moment in *What Price Glory*, when Sergeant Quirt, seeking the way out of a tight spot, turns to Captain Flagg and says, "Think fast, Cap'n."

At long last there are faint signs that the captains are thinking fast, that they are really trying to make sensible decisions and replace reflexes with cerebration, and inertia with action. What more obvious move than to take stock of the situation as a point of departure? Taking stock is not a matter of reading the daily paper by the individual, or reaction by the Government against each prod of aggression, the ultimate news for the individual and reaction by the Government being bacterial warfare or the big bomb. First and foremost, it means stopping the fiddling, at least of many foremost citizens and thinkers, while they give serious attention to the nation's and the world's problems and stop jigging to the ordinary music of their daily tasks. These problems can be solved neither by a Führer nor by

a brain trust composed of a haphazard selection of bright young men who happen to subscribe to the political faith of the party in power.

Two encouraging signs of a change that really began when America had to think fast with the first communist onslaught in Korea are the decision of the American Association for the Advancement of Science to sponsor a symposium on science and human values, during the last days of 1950 and the assembly plan recently announced by General Dwight D. Eisenhower at Columbia University. One subject for exploration by the Association at Cleveland is human ecology, with outstanding American scientists participating in a program whose honorary chairman is Roger Adams. The disciplines and experience brought to bear on the problem include those of Eduard C. Lindeman, Paul B. Sears, Rensis Likert, John E. Gordon, Marston Bates, M. L. Wilson, Otto Klineberg, George F. Davidson and Jean-Paul Harroy. At Columbia the plan is for an assembly of disciplined minds with widely varied training, in order to throw impartial light on the major problems that confront the nation and the world. The schedule calls for eight conferences a year, each lasting three to five days.

Americans will have come to grip with reality if only for a few days in Cleveland and on eight occasions during 1951 in New York. This is all to the good, but the Manhattan Project was not completed in nine meetings. It was implemented only by concerted, sustained and full-time effort. Thereby, physics, between 1941 and 1945, was moved forward fifty years. More important than physics is the science of human ecology, which deals directly with the "major problems that confront the nation and the world." The burning question is whether human ecology can be similarly advanced to keep pace with mankind's demonstrable capacity for overbreeding, underfeeding and destroying itself.

When will governmental agencies and universities stop fiddling and recognize their interdependent functions as institutes of theoretical and applied ecology running the year around to study and deal with the pressing present, rather than the prosaic past? After the first bomb? After World War III? The sand is running out. "Think fast, Cap'n."

MEDICAL INDIGENCE

BRAILEY, in a letter to the editor published elsewhere in this issue of the *Journal*, presents his own intelligent reflections on the problem of medical indigence and its social and economic implications.

It is true that the costs of medical care — especially of hospital care — have increased to a greater degree, in some particulars, than have the costs of certain other services and of various commodities and of many incomes. It is also true that the effectiveness of medical care has improved manyfold, even more spectacularly than has the quality of a number of the other necessities of life, excepting, perhaps, such products of man's ingenuity as the automobile, the television and various agents of destruction.

To say, however, that a person who cannot easily afford good medical care without due economy and careful budgeting is "medically indigent" is as absurd as it is to say that a person who has to buy his automobile or his television set on the installment plan or as the result of careful saving is indigent so far as transportation or home entertainment is concerned. Many of those who possess automobiles and television sets, who spend 20 cents a day or more for tobacco in addition to their expenses for liquor and the family addiction to cosmetics would nevertheless qualify by accepted standards for medical indigence.

The fact is that the trend toward a welfare state (perhaps halted or at least retarded as a result of the recent election) represents also a trend, observable in every quarter, toward easy indigence. "The State," according to a current, somewhat profane philosophy, "is my Shepherd; I shall not want."

There is such a thing as honest medical indigence, but it need not be as widespread as the apostles of the handout would have the country believe. Frugality, economy and adherence to a sound policy of financial independence would permit many a family to stay in the ranks of a self-reliant citizenry, who are now being encouraged to join those of the partially indigent.

The voluntary insurance plans, universally increasing in their popularity, have within them all the potentialities necessary to reduce medical indigence to its minimum and to remove in large part

the risk of overwhelming medical expense. The argument advanced by the proponents of compulsory so-called health insurance that the voluntary plans do not cover the total cost of illness is a compliment to the soundness of these plans. Organized as they are on an actuarial basis, total coverage, in itself not necessarily desirable, would entail too high premiums; complete coverage on a compulsory basis represents not insurance but taxation, and still further encourages indigence.

The vacuous term "indignity of the means test" is a pompous phrase coined by those who are in favor of pauperization, but without loss of face in the community.

OF MICE AND MEN

Much information, some of which has been commented on in the pages of the *Journal*, has come to light in recent months regarding the impact of rodent life on civilization, for better or for worse, and two practically synchronous news releases from such widely separated institutions of learning as Yale University and the University of Wisconsin serve to accentuate the drama of this relation.

From New Haven, in a mid-November release from the University News Bureau, comes the story of the murine stock farm that Dr. Leonell C. Strong, of the Yale School of Medicine, has been conducting since 1920. In that year Dr. Strong, then at the Cold Springs Harbor Laboratory of the Carnegie Institution of Washington, began breeding mice to ensure a supply of the timorous beasties for his own research on cancer.

Nature, carefully superintended and wisely directed, took its course. Mice, as pigs is pigs, is mice, and Dr. Strong's original pair has produced a line of 300,000 offspring, of which some 250,000 are pedigreed and genealogically recorded in the annals of their own unique kennel club.

Dr. Strong's mice have ventured the wide world over in the interests of research — to Madame Curie, for radiation tests, to Canada, Australia, Latin America, India, Great Britain, pre-war Russia and post-war Western Germany. In post-war Russia, where the laws of Mendel have been abrogated, they would naturally be of no value. They have moreover undergone two great mass migrations: in 1930, when they traveled by private freight car to Bar Harbor, Maine, and in 1933, when they made their most recent move, accompanying their breeder, friend and benefactor to New Haven, this time by truck.

A survey has shown that practically 50 per cent of the mice used in cancer research in the United States came originally from Dr. Strong's colony.

In Wisconsin, essentially a dairying state, the larger rodent, according to the University of Wisconsin News Service, is being ardently milked, drop by drop, in the interest of science to learn more about nutritional requirements for pregnancy and nursing. Studies that are underway in Dr. Conrad A. Elvehjem's laboratory seem to indicate that a deficiency in vitamin B_{12} is responsible for both lowered fertility and inadequate lactation in the rat.

The amount of B_{12} in rat milk varies with the type of protein the rat is fed, those eating beef having the largest amounts, those on a casein diet a moderate amount, and those that are pork fed having the least. Closely as the destinies of mice and men are linked, however, too close analogies cannot be drawn. Human beings do not always react like mice nor, equally fortunately, like rats.

Law, the colored lad that was bitten by a mad dog, died last week in Norfolk, whither he had gone to consult a mad-dog doctor.

Boston M. & S. J., *December 18, 1850*

The *Journal* lacks extra copies of the January 12, February 2, March 2 and 9, June 8 and July 27, 1950, issues. If any subscribers who do not bind their copies have the above-mentioned issues on hand, the *Journal* will pay 15 cents for each copy left at or mailed to its office (8 Fenway, Boston 15).

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

Bartol — John W. Bartol, M.D., of Boston, died on November 15. He was in his eighty-seventh year.

Dr. Bartol received his degree from Harvard Medical School in 1891. He was a former president of the Massachusetts Medical Society and the Boston Medical Library and a fellow of the American Medical Association.

His widow, two sons, four daughters, sixteen grandchildren and a brother survive.

BROWN — Sampson Brown, M.D., of Medford, died on October 7. He was in his fifty-third year.

Dr. Brown received his degree from Tufts College Medical School in 1928. He was a member of the courtesy staffs of Lawrence Memorial Hospital, New England Sanatorium in Winchester and Symmes Arlington Hospital and was a fellow of the American Medical Association.

His widow, two sons, a brother and three sisters survive.

GABLER — George L. Gabler, M.D., of Holyoke, died on August 28. He was in his eighty-second year.

Dr. Gabler received his degree from Long Island College of Medicine in 1902. He was formerly a member of the city board of health and a member of the staff of Holyoke Hospital and was a fellow of the American College of Surgeons.

A daughter, a son, two sisters and a brother survive.

GUSTAFSON — Paul Gustafson, M.D., of Cambridge, died on November 25. He was in his sixty-first year.

Dr. Gustafson received his degree from Harvard Medical School in 1916. He was chief of the Obstetrical Service at Mount Auburn Hospital and senior obstetrician at the Boston Lying-in Hospital and was a member of the New England Obstetrical and Gynecological Society and New England Pediatric Society and a fellow of the American College of Surgeons and American Medical Association.

A brother and six sisters survive.

MACDONALD — George H. MacDonald, M.D., of Everett, died on November 22. He was in his forty-eighth year.

Dr. MacDonald received his degree from Tufts College Medical School in 1928. He was a fellow of the American Medical Association.

His mother and a sister survive.

MURPHY — John A. Murphy, M.D., of Boston, died on December 2. He was in his thirty-seventh year.

Dr. Murphy received his degree from Tufts College Medical School in 1940. He was resident obstetrician at the Boston City Hospital and a member of the New England Obstetrical and Gynecological Society.

His widow and his parents survive.

ROBERTS — Oscar B. Roberts, M.D., of Baldwinsville, died on October 29. He was in his seventy-fourth year.

Dr. Roberts received his degree from Medico-Chirurgical College of Philadelphia in 1899. He was a member of the Henry Heywood Memorial Hospital in Gardner.

His widow, a son and a daughter survive.

TOUMEY — James W. Toumey, Jr., M.D., of Dedham, died on October 18. He was in his fifty-first year.

Dr. Toumey received his degree from Columbia University College of Physicians and Surgeons in 1926. He was an orthopedic surgeon on the staff of the Lahey Clinic and was a member of the American Orthopaedic Association and a fellow of the American Academy of Orthopaedic Surgeons, American College of Surgeons and American Medical Association.

His widow, a daughter and a son survive.

BOSTON MEDICAL LIBRARY

MIDDLESEX MEDICAL ASSOCIATION

The *Records* of the Middlesex Medical Association, kept from 1788 to 1798 and from 1813 to 1816, have been received by the Library, the gift of Mrs. Georgie Fiske Jackson, great-granddaughter of Dr. Joseph Fiske, Jr., of Lexington, an early member.

When the original group of physicians met in Concord on November 10, 1788, Oliver Prescott was chosen chairman, and Joseph Hunt secretary. Benjamin Waterhouse was a prominent member, and the others — in many cases names that still find representation in the medical profession — were Timothy Minot, Josiah Bartlett, Ebenezar Starr, William Bowers, Isaac Hurd, Timothy Harrington and Oliver Prescott, Jr. Waterhouse, professor of physic at Harvard University, and Bartlett were requested to obtain the records of the Suffolk Association, founded a short time before, and to draw up rules and regulations for Middlesex. The training of young men for medicine was much in the minds of all present at the initial meeting, and Waterhouse and Bartlett were urged, in making up the rules, to "point out a better method of educating Pupils in the practice of physick."

The day of the second meeting, the second Tuesday in December, proved to be stormy, and the meeting was postponed for twenty-four hours. A small group of the hardy and faithful met at Oliver Brown's Tavern; Prescott, Waterhouse, Minot, Bartlett and Hunt were present, and they "proceeded to business." Waterhouse and Bartlett brought in a complete constitution of twenty sections, which was read and voted upon, section by section. Amendments were made, and the whole adopted and ordered printed. The constitution appears in the *Records* in its final form, somewhat at variance with the printed edition. After it are the signatures of all the members, some obtained at a later date, for only 5 were present at the second meeting, once abandoned "by reason of inclement weather." In addition to the 10 names noted as attending the first meeting, there are signatures of William Gamage, John Hay, Sam Whitwell, John Batt, T. L. Jennison, Leonard Williams and J. Brooks. Cephas Prentice, Joseph Fiske, Jr., and Amos Cotting were recorded as not of Middlesex County. James Winthrop and Ezra Ripley were listed as honorary members, and further regular members to sign were Charles Whitman, Sylvanus Plympton and Amos Bancroft.

In reading the constitution of this singularly earnest group of general physicians, inspired by the newly won liberties of the Revolution, an impression is gained that the problems of 1788 were not far from those facing the medical profession today. Raising and maintaining the highest qualities of medical education and practice were the two fundamentals given most consideration. In Waterhouse's sonorous phrases — for it is assumed that he wrote most of the Constitution — "As health is a blessing which sweetens all enjoyments and long life that which all men naturally desire, so he who labours to teach his Fellow creatures how to secure the one and to attain the other, may

justly be numbered among the benefactors of mankind." In order to educate the future "benefactors of mankind," the Association strongly urged a uniform course of study at the "University of Cambridge," preceded by a basic knowledge of Latin and Greek, with at least an ability "to translate them by help of a dictionary." It was only from such a system, the final paragraph states, "that quackery can be banished from the land and the honest physician rise to usefulness and eminence."

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS

The January schedule for Consultation Clinics for Crippled Children in Massachusetts under the provisions of the Social Security Act follows:

Orthopedic Clinics	Date	Clinic Consultant
Haverhill	January 3	William T. Green
Greenfield	January 4	Charles L. Sturdevant
Lowell	January 5	Albert H. Brewster
Salem	January 8	Paul W. Hugenberger
Gardner	January 9	Carter R. Rowe
Brockton	January 11	George W. Van Gorder
Springfield	January 16	Garry deN. Hough, Jr.
Pittsfield	January 17	Frank A. Slowick
Worcester	January 19	John W. O'Meara
Fall River	January 22	David S. Grice
Hyannis	January 25	Paul L. Norton

Rheumatic Fever Clinics	Dates
North Reading	January 2, 9, 16, 23, 30
Fitchburg	January 3, 10, 17, 24, 31

Plastic Clinics	Consultant
Eastern Massachusetts	Bradford Cannon
Semi-monthly	
Western Massachusetts	Joseph M. Baker
Monthly	

Physicians referring new patients to clinics should get in touch with the district health officer to make appointments. Patients are seen by appointment only.

CORRESPONDENCE

WHY "MEDICAL INDIGENTS"?

To the Editor: In all the discussions concerning the distribution of medical care, there appears to be widespread agreement that an ever-growing proportion of the citizenry is becoming medically indigent. One wonders just how accurate this concept is and whether such medical indigents constitute a group so large as to justify a revolution in American medicine.

One can easily cite a hundred examples of diagnostic and therapeutic procedures unknown fifty years ago that make modern care more expensive than it was at the turn of the century. However, the rise in family incomes during this period has also been striking. Then, too, some medical costs have decreased rather than advanced. In 1900 the American family had to anticipate a good deal of illness that either no longer occurs or is more promptly cured by modern methods. For example, the treatment of pneumonia today is very much less costly than it was even twenty years ago.

It is certainly true that the occasional severe and prolonged illness constitutes a devastating financial drain, but does anyone know the average annual cost to the average citizen of the medical care that he is now getting or the estimated average annual cost of ideal medical care to the average citizen? The sums surely would not be astronomical. One wonders if they would prove to be greater or as great as what the average citizen pays for such things as tobacco, liquor and cosmetics. Tobacco, liquor and cosmetics do much to solace the weary heart, but if a choice must be made, should these pleasant indulgences take precedence over the cost for the care of one's health? On every day in every clinic one sees citizens who "cannot afford to pay the doctor" or the hospital, but I personally have never met a nonsmoker who refrained from smoking because he could not afford it.

Is not the difficulty that good medical care is valued too lightly? Might not a program of more effective education persuade the average American to place good health higher on the list of things for which he is willing to pay? One wonders if the problem of medical indigence is not largely a problem of medical indifference, but if voters refuse to be persuaded and if they finally insist that medical care be made a public service, at least reasons should be called by their right name and improvidence and indifference should not be permitted to masquerade under the more pitiful guise of indigence.

Allen G. Brailey, M.D.

Brookline, Massachusetts

DEPRIVATION OF LICENSE

To the Editor: At the meeting of the Board of Registration in Medicine held November 16 it was voted to revoke the registration of Dr. Manford R. Spalding, of Worcester, Massachusetts.

George L. Schadt, M.D.
Secretary

Board of Registration in Medicine
State House, Boston

BOOK REVIEWS

The Principles and Practices of Rehabilitation. By Henry H. Kessler, M.D., Ph.D. In collaboration with other authors. 8°, cloth, 448 pp., with 132 illustrations and a colored plate. Philadelphia: Lea and Febiger, 1950. $9.00.

Rehabilitation is an ameboid concept, spreading and undifferentiated, its pseudopods continually reaching out for new areas to explore or exploit, to divide or devour. Since the war years it has become a fashionable word, vague and too well publicized. In fact, its public-relations aspect may be its undoing, for as a result of its overstatement many have found it an excellent band wagon to board and have used the word to mean treatment, or simply as a synonym for the practice of medicine. In an attempt to be more comprehensive than previous writers, some authors have searched for new areas to include, and have wandered off a very broad way. Dr. Kessler, whose name has been identified more closely, and for longer, with the progress of rehabilitation than anyone in this country, is guilty of this charge. He invited chapters on plastic surgery and other unnecessary subjects that could have been omitted in the interest of good reading and a lower price.

Many of the 21 contributors have gained their knowledge from experience in the fields they discuss, and some of the chapters are outstanding. The statement on poliomyelitis by Bennett, of Warm Springs, Georgia, is the best available, and the practical value of Odoroff's approach to vocational rehabilitation makes rewarding reading. The rehabilitation of deaf patients is covered with unusual clarity by Marcus and Lederer, and Hudson's sound appraisal of work with the tuberculous helps to make this book the best in the field.

Principles and Practice of Plastic Surgery. By Arthur J. Barsky. 4°, cloth, 499 pp., with 1029 illustrations. Baltimore: Williams and Wilkins Company, 1950. $10.00.

In recent years an increasing number of books on plastic and reconstructive surgery have been published. This is undoubtedly due to the increasing number of civilian and wartime injuries, which the surgeon is called upon to treat with the hope of minimizing subsequent deformities. The

author of this book draws on his vast experience in the field of plastic surgery. He limits his description of procedures to those based on his practice and clinical experience.

The first 6 chapters are based on the fundamentals of plastic surgery including a discussion of free grafts and pedicled flaps of different types with their indication. The next 3 give the regional application described in the previous chapters. These include corrective surgery of the orbit, nasal deformities, malformations of the ear and the treatment of harelip and cleft-palate problems. The treatment of deformities of the neck, the extremities and the hand, of congenital as well as traumatic origin, is discussed in 3 chapters. The chapter on fractures of the facial bones, maxilla and mandible is brief in comparison with many of the others.

The scope of the subject has become so broad that it is not expected that all the variations of an operation can be included. The main value of this book is the description of the operations with which the author has had personal experience.

At the end of each chapter one finds a well chosen bibliography. The book is well illustrated and contains many clear diagrams. It should be a good source of reference to the plastic surgeon as well as the general surgeon.

Visual Development. By J. H. Prince, F. R.M.S., F.Z.S., F.B. O.A., F.S.M.C. Vol. 1. With a foreword by Professor H. Hartridge, M.A., M.D., Sc.D., M.R.C.P., F.R.S. 8°, cloth, 418 pp., with 190 illustrations. Baltimore: Williams and Wilkins Company, 1949. $9.50.

In the presentation of a two-volume work on visual development the author admits a 50,000 mile Odyssey to obtain information at the source. With 190 illustrations, and with expert handling of the source information, the author presents an authoritative and at the same time an interesting treatise on the comparative embryology, anatomy, and physiology of the visual mechanism in invertebrates and vertebrates.

From the single "eye spot" in Euglena, the author describes more and more complex visual organs until he reaches the visual mechanism of the primates. In man, the 130,000,000 rods and the 7,000,000 cones of the retina must relay their messages through 800,000 optic-nerve fibers leading to the visual cortex. Birds have derived a rich visual inheritance from their ancestors the Dinosaurs, and to facilitate extra keen vision birds have slender, highly differentiated cones, and they have plural maculae. The author discusses "booster" mechanisms at work in the retina, the close relation between visual purple and vitamin A, the process of photochemistry, the rods and cones of the retina and the process of dark adaptation. He alludes to the tapetum in certain animals that makes the eyes "shine" at night, to the pecten, which is found in birds, and to luminous "eyes" of deep-sea forms of life.

Volume II is in the course of preparation. The companion volumes would grace the library of any physician, and they would provide him with information not to be had easily from other sources.

Histology. By Arthur W. Ham, M.B. 4°, cloth, 756 pp., with 445 illustrations. Philadelphia: J. B. Lippincott Company, 1950. $10.00.

This is the latest in a long series of noteworthy English texts in histology since the time of Minot and Lewis. Scientifically unimpeachable, it is written by the professor of anatomy in the University of Toronto, known also as author, with Dr. M. D. Salter, of *Doctor in the Making.* Dr. Ham writes particularly from the didactic standpoint of the problems of learning and remembering, which present special difficulties to the medical student at this early stage in his experience. Over nine tenths of the 445 illustrations, including four plates in color, are new or original and are planned especially for visual teaching and to aid in the problems of tridimensional visualization. The author's interest in pathology has also led him to pay particular attention to the histology of arteriosclerosis, arthritis, cancer and diabetes. Each of the thirty chapters is followed by an abundant and well chosen bibliography of references. This volume is a memorable Canadian contribution to the literature of histologic teaching.

Clinical Therapeutic Radiology. U. V. Portmann, M.D., editor. 8°, cloth, 747 pp., with illustrations. New York: Thomas Nelson and Sons, 1950. $15.00.

This work outlines the treatment of cancer and allied diseases in a clear, concise and highly scientific manner. Dr. Portmann and his fifty-three associate authors have produced an excellent guide in this all-important field of cancer therapy. It represents a milestone in the field of therapeutic radiology and should be in the hands of every therapeutic radiologist and every person training in this field. Likewise, the oncologist and surgeon will find valuable information, which will help them determine the proper treatment for any given neoplastic process. The treatment of benign disease by irradiation therapy is also adequately covered. One of the dangers of a compendium type of book is the overlapping of subjects by different authors and the disagreement on methods of treatment. This has been held to a minimum in this book.

There are forty-one chapters, each of which deals with a separate entity. The book opens with a chapter on radiation protection and proceeds to the preparation of radon, the biologic effects of radiation and the radiosensitivity of tumors. Subsequent chapters deal with the treatment of every known neoplastic process that can be either cured or palliated by radiation therapy. Special attention has been devoted to lesions that are curable and the methods of treatment have been carefully detailed. Outstanding are the chapters on tumors of the testis and carcinoma of the cervix. The chapter on supervoltage irradiation is well presented, and includes the physical aspects of this new weapon. Concluding chapters deal with hormonal alteration of neoplastic disease, the production and use of radioisotopes and the care of patients receiving irradiation therapy. The final chapter is devoted to the literature of radiologic physics and is a valuable reference source.

The text has good illustrations, together with adequate author and subject indexes. Each chapter is followed by an excellent bibliography pertaining to its specific content.

Tuberculosis: A global study in social pathology. By John B. McDougall. 8°, cloth, 455 pp. Baltimore: Williams and Wilkins Company, 1949. $6.00.

In a fast shrinking world when the earth can be encompassed in a mere few days, it is inevitable that one's entire thinking, whether it is political, economic or social, should assume global proportions. This is no longer a mere dream of the visionary or professional "do gooders," but that of practical men as evidenced by President Truman's Point Four Program as well as the many activities of the United Nations.

Like wars tuberculosis is the common enemy of all mankind and has from time immemorial left its ravages upon the earth. Local programs to combat tuberculosis will have little or no effect unless an over-all plan is evolved to eradicate it over the world. The tubercle bacillus knows no boundaries, and counties in Minnesota cannot erect a fence against the invasion of the tubercle bacillus, no matter how intensive their campaign may be.

Thus, it is quite welcome that a book has been written on a global study in social pathology of tuberculosis. The author is well qualified to deal with this problem, since he grappled with this disease for many years as a clinician as well as adviser to UNRRA.

The four parts of the book give an over-all statistical account of the mortality rates in different countries, factors influencing morbidity and mortality, communal problems of this disease and finally practical considerations of the entire problem. The author makes a strong plea for the adoption of some standardized form of recording basic data that may help governments and fill the need for further intensive epidemiologic study. The value of this book is not so much in its content, since very little new material has been added, or for that matter even recommended, to existing information in the campaign against tuberculosis as in focusing attention on a global outlook. Local campaigns and close examination of all immigrants arriving here will not guard Americans against this disease, so long as the tubercle bacillus and substandard living conditions exist anywhere in the world. The book should be on the shelves of the private libraries of all public health officials, especially those interested in the epidemiology and public-health aspects of tuberculosis.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Cytologic Diagnosis of Lung Cancer. By Seymour M. Farber, M.D., Milton Rosenthal, M.D., Edwin F. Alston, M.D., Mortimer A. Benioff, M.D., and Allen K. McGrath, Jr., M.D., from the University of California Medical Service and the Department of Pathology, San Francisco Hospital and the San Francisco Department of Public Health. 4°, cloth, 69 pp., with 60 illustrations. Springfield, Illinois: Charles C Thomas, 1950. $6.00.

This atlas of 9 colored plates, with descriptive text and preliminary discussion of the subject, is well done. A bibliography of 98 references is appended to the text. The volume should be in all collections on cancer and on diseases of the lungs.

Transactions of the American Goiter Association: 1949 annual session, May 26, 27, 28, Hotel Loraine, Madison, Wisconsin. 4°, cloth, 460 pp., with illustrations. Springfield, Illinois: Charles C Thomas, 1950. $10.50.

This volume presents the papers read at the twenty-sixth annual meeting of the American Goiter Society. Some of the papers were previously published in the *Journal of Clinical Endocrinology*, but a number appear here for the first time. The Van Meter Prize essays are published, and it is interesting to note that the prize was awarded to Dr. William McK. Jefferies, of Boston, and that the first honorable mention went also to a Boston physician, Dr. Malcolm M. Stanley. The lack of an index detracts from the reference value of the volume (a table of contents cannot be considered the equivalent of a good index). The volume is essential to all medical libraries and should be available to all persons interested in endocrinology.

The Nature of the Bacterial Surface: A symposium of The Society for General Microbiology, April, 1949. Edited by A. A. Miles and N. W. Pirie. 8°, cloth, 179 pp., with 12 plates. Springfield, Illinois: Charles C Thomas, 1950. $3.00.

This symposium was held in London, and 27 chemists, physicists and biologists participated in the meeting. The printing was done in Great Britain, and the volume is well published. The book should be in all collections on bacteriology.

A Manual of Bandaging, Strapping and Splinting. By Augustus Thorndike, M.D., associate in surgery, Harvard Medical School, and chief surgeon, Department of Hygiene, Harvard University. Second edition. 12°, cloth, 148 pp., with 119 illustrations. Philadelphia: Lea and Febiger, 1950. $2.00.

This second edition of a well illustrated manual has been revised to conform to the experience gained from World War II. The book is designed for the use of medical students, pupil nurses and hospital orderlies. It could be used in part as an advanced first-aid manual. The material is well organized, and the publishing is excellent.

Thomas W. Salmon, Psychiatrist. By Earl D. Bond, M.D. With the collaboration of Paul O. Komora. 8°, cloth, 237 pp., with 6 illustrations. New York: W. W. Norton and Company, Incorporated, 1950. $3.00.

Dr. Salmon was a pioneer in the field of mental hygiene. He took part in the founding of the National Committee for Mental Hygiene and became its medical director, and was chief of psychiatry for the A.E.F. in World War I. The text is well written in a narrative style. A list of his writings is appended to the text. The volume is well published and should be in all collections on psychiatry and in medical and public libraries.

NOTICES

MASSACHUSETTS SOCIETY OF ANESTHESIOLOGISTS

The third session of the annual postgraduate education course of the Massachusetts Society of Anesthesiologists will be held in the Bigelow Amphitheater of the Massachusetts General Hospital, Boston, on January 6, from 2:30 to 5:00 p.m. The subject of the course will be "Pathology of the Cardiovascular System and the Physiologic Changes that Would Influence the Conduct of Anesthesia." Samuel Gilman, M.D., of the New England Center Hospital, Boston, will be chairman.

PROGRAM

Physiology in Valvular Heart Disease as Related to Anesthesia. Samuel Gilman, M.D.
The Pathologic Physiology of the Coronary Circulation as Related to Anesthesia. A. Abrams, M.D.
Cardiac Arrhythmias. A. Finck, M.D.

The Massachusetts Society of Anesthesiologists will meet in the Auditorium of the Nurses Home, St. Vincent Hospital, 73 Vernon Street, Worcester, on January 9, at 7:30 p.m. The program will be as follows:

Electrical Activity of the Cortex in Relation to Its Metabolism. Hudson Hoagland, Ph., Sc.D., executive director, Worcester Foundation for Experimental Biology; research professor of physiology, Tufts College Medical School.
Pathology of Cerebral Anoxia. Albert Scheflen, M.D., clinical director, Worcester State Hospital; and David Rothschild, M.D., director of laboratories, Worcester State Hospital.
Chemistry and Physics Related to Explosive Limits of Inhalation Agents. Maurice E. Smith, M.A., Ph.D., professor of chemistry, Worcester Polytechnic Institute.

SPRINGFIELD ACADEMY OF MEDICINE

A meeting of the Springfield Academy of Medicine will be held in the Woman's Club Building, 43 Spring Street, on Tuesday, January 9, at 8:30 p.m. Irving S. Wright, M.D., professor of clinical medicine at Cornell University Medical College, will speak on the subject "A Critical Evaluation of the Present-Day Treatment of Peripheral Vascular Diseases."

BETA IOTA CHAPTER OF NU SIGMA NU

The Beta Iota Chapter of the Nu Sigma Nu Fraternity announces the annual Rudolph Matas Lecture, to be held in Dixon Hall, Tulane University of Louisiana, of New Orleans, Louisiana, on February 9 at 8 p.m. Dr. Frank H. Lahey, of the Lahey Clinic, Boston, will be the guest lecturer.

Members of the medical profession are cordially invited to attend.

NEW ORLEANS GRADUATE MEDICAL ASSEMBLY

The fourteenth annual meeting of the New Orleans Graduate Medical Assembly will be held in New Orleans from March 5 to 8, 1951, with headquarters in the Municipal Auditorium.

The program will include a panel discussion on ACTH and Cortisone, color television presentation of surgical and medical procedures, a series of lectures on neoplastic disease and trauma, clinicopathological conferences and three round-table luncheons (all-inclusive registration fee, $15). Nineteen outstanding guest speakers will participate in the Assembly. A postclinical tour by plane to Panama, Colombia, Ecuador and Peru will be conducted from March 10 to 25.

Further information concerning the meeting and the tour may be obtained from the Secretary, New Orleans Graduate Medical Assembly, Room 103, 1430 Tulane Avenue, New Orleans 12, Louisiana.

(*Notices concluded on page xv*)